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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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Norman Stockbridge, M.D.
Robert Temple, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. HARRINGTON: Good morning and welcome to this meeting of the Cardio-Renal Advisory Panel. My name is Bob Harrington from Duke University. I will be the Acting Chair today filling in for Bill Hiatt.

The first order of business is to go around and start the introductions. So, Norm, why don't I start with you and go around the table.

DR. STOCKBRIDGE: I am Norman Stockbridge. I am the Director of the Division of Cardiovascular and Renal Products at FDA.

DR. TEERLINK: I am John Teerlink from the University of California/San Francisco and San Francisco V.A. Medical Center.

DR. LINCOFF: I am Michael Lincoff from the Department of Cardiovascular Medicine, The Cleveland Clinic Foundation.

LCDR GROUPE MILLER: Cathy Groupe Miller with the FDA Advisors and Consultants Staff.

DR. PAGANINI: I am Emil Paganini, The

Cleveland Clinic Foundation.

DR. HSU: Jason Hsu, Department of Statistics, Ohio State University.

DR. WARNER STEVENSON: Lynn Warner Stevenson, Brigham and Women's Hospital, Cardiovascular Division, Boston.

MR. FINDLAY: Steve Findlay from Consumers Union. I am the Consumer Representative on the panel.

DR. RYDER: Steve Ryder. I am the Industry Representative, non-voting, sitting in for my friend, John Neylan, who gives his regrets and couldn't make it.

DR. TEMPLE: Bob Temple, ODE-I Director.

DR. HARRINGTON: I am just going to remind the panel that I have been told that only three mikes can be live at any one time to try to keep shouting to a minimum, so if you could just keep that in mind.

I have one announcement to read and then I will turn it over to Cathy.

Today's meeting we will have a lot of

discussion, which will result in recommendations at the end of the day for the Food and Drug Administration. 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.

At that time, the FDA will hold a press briefing for members of the credentialed media to discuss the recommendations from the committee and take any questions that they may have.

Conflict of Interest Statement

LCDR GROUPE MILLER: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a

conflict of interest with the following exceptions.

In accordance with 18 USC 208(b)(3), Dr. Robert Harrington has been granted a waiver for the following personal and imputed financial interests.

Dr. Harrington is an ad hoc consultant to the sponsors for Avalide and a competitor on unrelated matters. The compensation from each sponsor is less than $10,001 per year and between $10,001 to $50,000 per year from the competitor. Dr. Harrington donates these consulting fees to educational charities. His employer, the Duke Clinical Research Institute, has an interest in a competitor. The Institute receives more than $300,000 per year for participating in a study of a competing product.

Dr. John Teerlink has been granted a waiver under 18 USC 208(b)(1) for the following personal financial interests. Dr. Teerlink serves on a competitor's unrelated steering committee for which he receives less than $10,001 per year.

He is a blinded endpoint reviewer for a study involving a component of Avalide and receives

between $10,001 to $50,000 per year from the sponsors. Dr. Teerlink also owns shares of a health sector mutual fund, valued between $50,001 to $100,000.

Waiver documents are available at the FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Steven Ryder is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Ryder's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Ryder is employed by Pfizer. Pfizer makes a competing product to Avalide.

In the event that the discussions involve

any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from the discussions and their exclusion will be noted for the record.

With respect to all other participants, we ask that in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. HARRINGTON: Norm, you are next up on the agenda.

Introduction and Background

DR. STOCKBRIDGE: Good morning. I first wanted to note that this would have been the last meeting for three members whose term is scheduled to end on June 30th of 2007. None of these people are here, but the retiring members would be Ronald Portman, who has in fact resigned from the committee, Dave DeMets, and Bill Hiatt.

Despite the fact that they are not here, I

would hope that everybody would join me in a round of applause for their public service.

[Applause.]

I also want to acknowledge a new member, Emil Paganini. I appreciate his coming to this. In addition, we are joined today by two temporary members, Jason Hsu and Steven Ryder. I appreciate their participation, too.

I want to take just a minute and sort of describe for you the broader context of this meeting. It is one of a series of things we have been doing with antihypertensive drugs over the last year and something.

We began with a meeting to discuss the idea of putting outcome claims in labeling for antihypertensive drugs. The draft guidance for that is still circulating around at FDA. I am hopeful that it will make it into a public comment period and a Federal Register Notice sometime this spring.

We also last year had a meeting to discuss the outcome events in placebo-controlled trials as

a way of thinking about whether or not it was still okay to use placebo in antihypertensive drug development trials.

That meeting resulted in some advice that we should probably try to keep the double-blind period of such trials pretty short, and we will certainly be doing that. I do not anticipate any formal guidance coming out of that.

This is the first of what will probably be several meetings to discuss the use of combination products, combination antihypertensives. This meeting is to discuss whether or not to allow a first-line use claim with sort of minimal claims associated with it.

There will probably be a later meeting. I have got staff going back through the factorial trials that got many of the combination products approved in the first place, to look at the adverse event rates sort of by millimeter of mercury achieved to try and be the basis for a discussion about what the threshold might reasonably be for introducing a second drug. So, somewhere down the

road, we will probably be talking about that.

Then, the last thing that is sort of on a long-term agenda is to question the basis by which we make decisions about when to up-titrate people in practice to address the rationale behind the instructions for use in antihypertensive drugs. So, somewhere down the road, we will probably be having that conversation. There is a sort of hint to it in one of the questions in today's meeting.

This meeting is a little bit unusual in that, ordinarily, the sponsor wants something, the FDA is the most conservative party in the room, and the advisory committee tends to find a place that is somewhere in between.

This meeting has some different feel for it. The proposal to actually consider this as a basis for approval. The Avalide decision, came from Bob Temple and me, so the committee's role here is to assume more of the conservative role and try to figure out why, if at all, we might want to think further about this rather than rushing forward.

Thank you.

DR. HARRINGTON: Bob, did you have any opening comments?

DR. TEMPLE: Only one, and this is covered in the questions. As Norman said, the labeling for combination antihypertensives has been, on the whole, conservative. It says use this if the single entity fails, what you might call the idea of step care. That is sort of how it worked.

But even in the antihypertensive community, step care is breaking down a little bit, you don't necessarily want to push the dose of the diuretic to the largest dose. That became obviously sometime ago. So, people are moving to combined therapy earlier.

Our standard, as the questions say, had been if you can find a population, if you can identify a population, that has very little chance of getting to an appropriate goal with a single entity, we would for that population kind of play with the idea of using two drugs as initial therapy.

As we began to look at these data, what we realized is that you may not find a population of which only 10 percent respond to the single entity but, within any population, you can identify subsets who have very little chance of responding, because the people have varying starting blood pressures of either diastolic or systolic.

So, what we are talking about now is whether we should be presenting the results of those trials and telling people use your judgment. If you have a person who is unlikely to get to the goal--and here is the data on what fraction people get to the goal--is it reasonable to start those people on more than one drug.

As Norman said, we are being relatively aggressive on this. I think we are thinking that hypertension isn't treated aggressively enough on the whole to having a little public-health hat on, so that is what our thinking is, and we thought it would be good to discuss all of this publicly.

DR. HARRINGTON: That is a good introduction and I think sets the tone for what

should be an interesting day.

Open Public Hearing

We are going to start the open public hearing. Before we do that, I am required to read the following remarks.

Both the FDA 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 that 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 relationship 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 this 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.

With that as the opening remarks, I will turn it over to Dr. Tom Giles from Tulane to start the Open Public Hearing session.

DR. GILES: Good morning. I see I have two mikes, so if one more mike goes on, I can be killed.

I do appreciate the opportunity to speak with you this morning about a topic that I personally find very challenging. I am actually encouraged by the remarks of Drs. Stockbridge and Temple this morning.

[Slide.]

I will start with my disclosures. I am sponsored here today by Novartis. They are paying my travel, my lodging, and breakfast at the Best

Western. These are my disclosures relative to grant support. As regards Novartis, I do serve as a consultant for them and actually have research grant support from them.

[Slide.]

I would like to spend my few minutes in sort of outlining for you what I think would be some points for consideration relative to the use of fixed dose combinations in rather a wide range of people who have hypertension.

Now, what is displayed on this slide is the relationship, on the left, of blood pressure to adverse cardiovascular outcomes. This was sort of the original observational data. Notice I said blood pressure because, as I go through here, I will make a little bit of distinction between blood pressure as a physical force and hypertension as a disease.

Borne out of those data, an hypothesis was generated that if you lowered blood pressure, that benefit would accrue, and those data are shown on the right in the classic Veterans Administration

Study No. 2, very clear-cut, lower blood pressure, benefit.

[Slide.]

Now, as a result of that and what ultimately became sort of stepped care therapy, we got some interesting tools. As a matter of fact, we got a triple combination product approved by the FDA for the management of blood pressure in people who had hypertension and elevated blood pressures.

Some of you in the room may be a little bit too young to remember this, but this was actually the best selling antihypertensive drug combination in the United States of America. It included hydrochlorothiazide, Esidrex, hydralazine, which was Apresoline, and Serpasil or reserpine. So, it was Ser-Ap-Es, or Ser-A-Gen, or Seralazide, or Serpazide, but there were various combinations.

This was a tool. Now, why was this tool important? Because it lowered blood pressure. It did it in a predictable fashion with a predictable adverse outcome. And I think we can all take some pride in the fact that, using tools such as this,

that over the years, we have been able to accomplish some good things.

[Slide.]

I think the Agency, industry positions, everybody realizes that we have reduced stroke, we have reduced major cardiovascular events, and we have reduced CV death. Everybody also realizes that we have a long way to go.

Now, one of the reasons I believe that we have not done better is that we have not brought blood pressure down to optimal levels among people with hypertension, and we are still learning about where that is.

[Slide.]

I submit that the data that I am showing you here is one of the signal observations made in the last several decades about blood pressure in its relation to cardiovascular risk. These are data from Sarah Lewington and her colleagues in the UK. A million observations, people over the age of 40 followed prospectively, and these are the data.

Cardiovascular risk begins when the blood

pressure begins to exceed optimal 115/75 and doubles for each 20/10 mm of blood pressure increment. I want you to notice that this is linear, that there is absolutely no threshold in this. There is no break point in here where you can go from being sick to being well as identified by that curve and, for older people, this curve is actually log-linear.

I would also suggest to you that the notion that you can necessarily come down on this curve is something that always requires clinical data.

[Slide.]

Nevertheless, a 10 mm reduction in systolic blood pressure would reasonably account for a 30 percent reduction in risk of ischemic heart disease mortality and a 40 percent reduction in risk of stroke, which is clearly the most pressure-sensitive adverse outcome from hypertension.

[Slide.]

We do have clinical trial data, most of

it, and a lot of it shown here. You can probably recognize maybe some of your most favored acronyms. What it shows on the horizontal axis in these trials is a difference between the experimental treatment blood pressure reached compared to control and systolic blood pressure, and on the vertical axis, the odds ratio for cardiovascular outcomes.

I think it is pretty clear that that curve is continuing to improve even with a reduction of 25 mm of mercury systolic, which, as I am sure this group knows, is the number one target for management of people with hypertension, systolic blood pressure, not the diastolic.

[Slide.]

There is hardly any clinical trial of people who have hypertension that is conducted with monotherapy. It just hardly exists, and the reasons for that are fairly clear. Most patients who have this disease, even in controlled clinical trial setting, require more than one drug. As a matter of fact, as you see down there in the IDNT

trial, trying to get systolic blood pressure less than 135/85, which was a diabetes trial, you are up to four drugs.

So, monotherapy, while it may be appropriate for some patients with lower ranges of blood pressure, for the vast majority of people with hypertension, it won't happen.

Now, having said that, I hope you recognize that virtually three-quarters of the strokes in this country occur in people whose blood pressure are less than 160/90, less.

[Slide.]

JNC 7 went a step further and suggesting that if you were really trying to get about a 20/10 mm mercury reduction, that you ought to start with two drugs. Why? Well, first of all, we now know from studies, such as VALUE, that you frankly don't have the luxury of waiting months to years in order to control blood pressure. The exposure for patients is simply to expose them to the risk of strokes and heart attacks.

Similarly, if you want to get down below

130/80, it will get you about 10 mm of mercury systolic for each drug component of your regimen. So, JNC 7 concluded the use of fixed dose combination may be more convenient and simplify the treatment regimen.

[Slide.]

I will close with some advantages and then some disadvantages perhaps.

What are the advantages of having initial fixed dose combination therapy? Well, clearly, if you are in the range of patients who have got Stage 2 by JNC 7 definition hypertension, it is clear that, in order to get those patients down below even 140/90, it is going to require at least two drugs.

On the other hand, you may be, in some combinations, able to achieve lower doses of each component and still get an impressive reduction in blood pressure which may improve tolerability and reduced adverse outcomes.

Simplified treatment regimens, patients like it better, they adhere to it better, and there

can even be some economic benefit; fewer copayments, health care costs reduced, and rapid reduction in blood pressure resulting in fewer office visits.

Moreover, we are into this whole area of responder/non-responder rates. We are not smart enough in the hypertension community yet to do what the infectious disease folks do. We haven't identified Helicobacter for ulcer. We don't know the pneumococcus for pneumonia. So we depend on multiple mechanisms of action to reduce blood pressure in our patients who have hypertension.

[Slide.]

Multiple mechanisms of action can be complementary, many times offsetting adverse side effects; for example, a RAS agent with a diuretic or a RAS agent with a calcium channel blocker, where, for example, the incidence of edema is less.

Predictability, that is the key. What does the physician want? They want a tool that produces a predictable response in blood pressure with a predictable adverse outcome profile. Armed

with that tool, physicians can make choices about how to treat their patients regardless of where their blood pressure starts. They will determine what level of blood pressure reduction they need that will provide them the tools to do it.

[Slide.]

Now, what are the disadvantages? Some people would argue, well, what if you could get by with monotherapy. There are patients perhaps in whom that can happen, and they will continue to get one drug. However, we now know the majority of patients are going to require at least two.

People worry about hypotension. What if you get somebody who has got a sudden high drop in blood pressure, will they suffer? Well, of course, we don't like precipitous drops in blood pressure, and we have taken account of that. We don't give bite-and-swallow nifedipine in the emergency rooms anymore. We have learned and we have better control of that.

How about additive risk for dose-independent adverse effects? The

idiosyncratic response, for example, of people that get angioedema with an ACE inhibitor is an example. However, there are, generally speaking, monotherapy components that are given as part of a multi-drug regimen, so a fixed dose combination really doesn't help that.

That has to be balanced against the risk that I showed you of adequate blood pressure reduction. If you do get adverse risk, generally, it is pretty obvious what the cause is. Mild edema, for example, with calcium channel blocker, calls for help with an ACE inhibitor, these are things we are all well aware of. Therefore, more office visits and more lab tests are not necessary.

[Slide.]

So, in conclusion, some thoughts. Blood pressure, when it rises above optimal, doubles the risk of cardiovascular adverse outcomes with the doubling every 20/10. It is linear with no threshold. Lower in every trial that we have seen is better, the PROGRESS trial being a great example. Normotensives reduce 10 mm of mercury

systolic, 30 percent reduction in recurrent stroke.

The majority of patients require at least two drugs to achieve blood pressure control and to support our friends on the JNC Committee for people where you want to at least reduce it 20/10, you are going to need at least two.

[Slide.]

Multiple combinations have been well studied, and I will emphasize again that the patient response to fixed dose combinations is predictable. A lot of this has to do with what the Agency has required sponsors to do, and that is they have to do particular factorial design studies to illustrate what the variable components in mixture can produce in terms of efficacy and side effects.

Incremental efficacy with good tolerability has been achieved with combinations representative of several antihypertensive classes, so you will see everything mixed, I think, in the future up to and including perhaps triple combinations.

The benefit/risk profile of these agents can be determined, I think, already from clinical studies to support clinical use.

So, with those remarks, thank you very much for your attention and for inviting me here.

DR. HARRINGTON: Thank you, Dr. Giles.

Before you leave, does anybody on the committee have a question?

[No response.]

DR. HARRINGTON: Thank you very much.

We are going to move to the sponsor presentation. We are a little bit ahead of schedule, which is fine. We have the rest of the morning devoted to sponsor presentation coupled with questions.

The way the program is listed is that there will be a series of presentations followed by questions. But, given that we have all the morning, if the panel is okay with it, I would like to be able to ask questions after each speaker so that the questions are fresh in our minds.

I will turn it over the group from

Bristol-Myers for introductions and then the series of presentations.

Sponsor Presentations

Bristol-Myers Squibb Company

Introduction

DR. WACLAWSKI: My name is Anthony Waclawski. I am the Vice President of Regulatory Sciences at Bristol-Myers Squibb.

[Slide.]

Bristol-Myers Squibb and Sanofi Aventis have collaborated to study Avalide for the initial treatment of severe hypertension. Our goal is to make available a therapy that delivers prompt and substantial blood pressure reductions with a minimal risk of syncope or hypotension.

[Slide.]

We are meeting today because FDA is reconsidering criteria for approving combination products for first-line use in hypertension.

The Agency has requested a review of the data supporting the first-line use of Avalide to aid in developing this paradigm. FDA is also

seeking input regarding appropriate labeling of combination products for initial use in hypertension.

[Slide.]

Avalide is a fixed-dose combination product composed of the angiotensin II receptor antagonist irbesartan and the thiazide diuretic hydrochlorothiazide.

Avalide was approved in the United States in 1997 and has accumulated about 10 million patient years of exposure worldwide. It is marketed in three dosage strengths.

Current Avalide labeling precludes use of the combination until it is shown that titration with one of the components does not adequately control blood pressure. This requirement for titration reflects the knowledge and regulatory practices at the time Avalide was approved.

[Slide.]

The underlying principle is that once a patient is treated with a single drug, the full dose, the full approved dose range of that drug

should be tested and assessed before adding a second drug. The intent is to avoid the potential side effects from a second drug unless it is needed to control blood pressure.

Although this may avoid unnecessary polypharmacy, it can also delay the control of blood pressure, allowing greater exposure to the risks to hypertension. The risks associated with delayed control have taken on greater weight as clinical practice and guidelines have evolved.

Several recent large clinical studies suggest that the greater reductions in blood pressure attained with a more effective initial therapy are difficult to match with titration and add-on strategies. The differences persist even in clinical studies with frequent visits and liberal use of additional therapy.

The general principles for labeling fixed-dose combination products for hypertension have been applied to almost all combination products. However, FDA approved three combination products for initial use when the data have

supported it.

[Slide.]

Capozide was approved for initial therapy because it allowed more convenient dosing. Instead of dosing two or three times a day, the combination could be given once a day.

Ziac was approved because the combination had fewer adverse events than the monotherapy doses that provided similar efficacy.

Hyzaar, the most recently approved fixed-dose combination product for first-line use in severe hypertension, was approved after showing that a large proportion of patients with severely elevated blood pressures were not controlled on losartan monotherapy.

Based on its substantial efficacy and tolerability profile, Avalide should also be approved for initial use.

[Slide.]

This is the proposed indication. Avalide is indicated as initial treatment of severe hypertension. This indication is strongly

supported by the Avalide program and focuses on patients with severe hypertension as these patients are likely to benefit most from initial combination therapy.

In the questions to the committee, FDA has listed alternative indications which differ in how they identify the patient population. We are open to discussion of the appropriate wording of the indication, and we look forward to the perspective of the committee regarding what language would be most appropriate and useful for clinicians in this regard.

[Slide.]

In all our presentations today, severe hypertension is defined as a systolic blood pressure greater than or equal to 180 mm of mercury systolic, or diastolic blood pressure of greater than 110 mm of mercury. Moderate hypertension is defined as a systolic blood pressure between 160 and 180, and a diastolic blood pressure between 100 and 110.

When our program was designed in 2003,

these definitions were drawn from the JNC 6 guidelines. The subsequent JNC 7 guidelines have merged moderate and severe hypertension into a broader category called "Stage 2 hypertension."

The current guidelines recommend initial combination therapy for all Stage 2 patients and specify that initial combination therapy should include a thiazide diuretic. The guidelines recommend starting with a combination to increase the likelihood of achieving a blood pressure goal promptly. They also recognize that most Stage 2 patients need at least two drugs in order to achieve blood pressure control.

Our presentation today will focus on severe hypertension or the upper range of what is now Stage 2 blood pressures.

[Slide.]

To evaluate Avalide for severe hypertension, we conducted two large studies.

The pivotal study was one of the largest studies ever conducted in severely hypertensive patients. Our supportive study in moderate

hypertension was conducted to provide additional data to evaluate the safety and tolerability of initial use of Avalide. Enrollment in the second study required baseline blood pressures that, according to current guidelines, might also be considered for initial combination therapy.

With this program, we set out to show that Avalide was effective in a population of patients very unlikely to be controlled by the irbesartan monotherapy. A regulatory precedent had defined "very unlikely" as 10 percent or less of subjects achieving a diastolic blood pressure of less than 90 mm of mercury. This approach had been used once before in the approval of Hyzaar for first-line use. Results of our study differed from those of the Hyzaar study.

[Slide.]

With irbesartan, 33 percent of subjects achieved a diastolic endpoint of less than 90 mm of mercury. Therefore, according to the criteria used to approve Hyzaar, our study did not identify a large proportion of patients very unlikely to reach

this diastolic blood pressure level with the monotherapy.

However, Avalide was still significantly more effective than irbesartan, achieving this endpoint in 47 percent of subjects. In addition, other measures of efficacy showed even larger relative differences.

With Avalide, 35 percent of subjects achieved the blood pressure goal of less than 140/90, but only 19 percent did with irbesartan. These differences resulted from a greater blood pressure reduction with Avalide of approximately 10 mm of mercury systolic and 5 mm of mercury diastolic. This efficacy advantage was obtained with a favorable tolerability and safety profile.

On the basis of these data, FDA issued an approvable letter for Avalide, proposing a new additional criteria for approving combination products for initial use in hypertension. This was supported by the following observations.

[Slide.]

First, current guidelines recommend

initial combination therapy for patients with severe hypertension.

Second, the Hyzaar precedent has limited usefulness, because it is based on a single arbitrary measure of monotherapy efficacy. Blood pressure response in such studies is a function of the study design, the patient population, and the endpoint.

For example, the Hyzaar study enrolled patients previously treated and uncontrolled with up to three drugs, and 80 percent had been treated and uncontrolled with at least one prior therapy.

In the Avalide study, subjects were previously treated with, at most, one drug, and almost one-half had not been previously treated at all.

The Avalide program has prompted consideration of a new criteria, one based upon the efficacy and tolerability of the combination, coupled with labeling that describes the relationship between baseline blood pressures and the expected response from the combination compared

to the monotherapy.

In clinical studies with Avalide, substantial additional efficacy was obtained with a tolerability profile similar to the monotherapy, and post-marketing safety data reflecting approximately 10 million patient years of exposure provide a reassuring safety profile.

[Slide.]

In the presentations that follow, we will review the data that support the approval of Avalide as an initial treatment for severe hypertension.

Because our proposed indication focuses on patients with severe hypertension, Dr. William Weintraub, Chair of Cardiology and Director of the Christiana Care Center for Outcomes Research, will begin with a review of some new data that addressed the risks of severe hypertension and the need for better treatment regimens in these patients.

Dr. Pablo Lapuerta, from Bristol-Myers Squibb, will then show how the Avalide data support approval for initial use in this population. He

will focus on the greater efficacy attained by the addition of hydrochlorothiazide to irbesartan and the safety of the combination, focusing on both the dose-dependent and the dose-independent side effects of hydrochlorothiazide.

Dr. Michael Weber, from SUNY Downstate College of Medicine, will show that there is a strongly positive benefit/risk ratio for Avalide as a combination therapy for initial use in the treatment of severe hypertension.

I will then return to conclude and moderate the question and answer portion of our presentation.

Thank you.

Dr. Weintraub.

DR. HARRINGTON: Before you go, let me just make sure that the committee doesn't have any questions.

Bob?

DR. TEMPLE: So, if you could identify people with only moderate hypertension, but who are, say, diabetic and whose goal according to

various experts should be less than 130/90, or it should be lower than that, you wouldn't think the drug should be recommended for them. It's all linked to severe is what your preferred outcome is, not likelihood of reaching goal?

I am being deliberately provocative, because the latter is the approach--

DR. WACLAWSKI: Our proposal has stayed close to the discussions that we have had with the Agency over the years including our initial intent for the program, but I do want to communicate to the committee that we are open to the discussion today on how it might impact the indication and the recommendation for how to communicate that to labeling.

So, we are open to that. But our presentation today is focused on severe hypertension because those patients are the ones that are going to benefit most from the combination therapy.

Unmet Need in Severe Hypertension

DR. WEINTRAUB: Thank you, Tony, and good

morning, everybody.

[Slide.]

Severe hypertension still remains an important problem. Severe hypertension is defined as systolic blood pressure greater than or equal to 180 mm of mercury, or diastolic blood pressure greater than or equal to 110 mm of mercury.

JNC guidelines endorse initial combination therapy for blood pressures greater than 160 systolic or 100 diastolic. In severe hypertension, the need for combination therapy is much greater. Severe hypertension still affects approximately 2.4 million people, and approximately 1 million of them are untreated.

[Slide.]

Severe hypertension leads to substantial morbidity and mortality. Severe hypertension can progress to hypertensive emergencies. These emergencies can consist of a variety of presentations with severe blood pressure elevations and acute end organ damage. The organ damage can include retinopathy, nephropathy, heart failure,

cerebral hemorrhage. With or without end organ damage, severe hypertension requires immediate and effective treatment.

In addition to these emergencies, there is a particularly high risk of cardiovascular events that includes myocardial infarction, stroke, and cardiovascular death.

The risk of these events is substantially reduced with prompt blood pressure lowering. The incidence of cardiovascular events is particularly high for patients with severe hypertension.

[Slide.]

The Framingham study showed a strong relationship between blood pressure and cardiovascular risk. The uncontrolled population, above 140/90, is already at significantly increased risk. However, the severe population, above 180/110, has such high event rates that problems, if sustained, blood pressure reduction is especially important.

Unfortunately, more recent data still show high rates of morbidity in patients with severe

hypertension.

[Slide.]

At Christiana Care Health System in Delaware, we are examining outcomes in patients with hypertension. From our outpatient electronic medical record, we have assembled a cohort of over 16,000 patients seen in primary practice. The EMR includes blood pressure data, as well as comorbidity and outcomes. From these data, we classified patients according to their maximum blood pressure as being normotensive, having mild or moderate hypertension, or severe hypertension.

We examined the outcomes in these patients from the index data defined by their maximum blood pressure. Outcomes data are available for all emergency room visits and hospitalizations along with ICD9 codes that will allow us to examine the primary diagnosis for each presentation.

In this population, we have identified over 2,000 patients with severe hypertension. At any given time, the prevalence of severe blood pressure elevations is low, but over the course of

several years, the cumulative incidence is substantial. That is why we have identified so many patients.

[Slide.]

These patients are much like patients across the United States with severe hypertension. They are more often African-American and have important comorbid conditions including diabetes and obesity. In these patients, an excess of emergency room visits and cardiovascular hospitalizations can be seen in just a short time frame.

[Slide.]

In just one year, we see 100 events per 1,000 patients, and the incidence continues to build over time. The Framingham heart study showed a very high risk of events many years ago, this risk remains today. There is a substantial opportunity to help patients with blood pressure control.

The outcomes we see go beyond heart attacks and stroke. They include presentations of

heart failure and other cardiovascular events.

[Slide.]

In particular, we see a dramatic increase in the incidence of heart failure in patients with severe hypertension compared to those with milder hypertension or individuals who are normotensive.

Compared to normotensive individuals, we see an almost 9-fold increase in the rate of events, and compared to mild and moderate hypertension, we see more than twice the incidence of events.

Part of the problem with severe hypertension is the difficulty in providing patients with adequate follow-up care. One might expect that physicians would treat severe hypertension much more aggressively than mild or moderate hypertension, but the data show the treatment remains inadequate.

[Slide.]

A study on actual practice at Veterans Affairs clinics examined titration patterns at clinics for hypertension. These analyses pertain

to a database of over 50,000 patients.

If a patient presents at a visit with a blood pressure level in the mildly hypertensive range, the physician will increase therapy about 20 percent of the time and schedule the next visit in about two months.

If a patient presents at a visit with blood pressure levels in the moderate range, the physician will increase therapy more often and schedule the next visit a bit sooner.

If a patient presents at a visit with a blood pressure reading in the severe range, the physician will increase therapy more often, but still only 40 percent of the time, and the next time the patient sees the doctor will be in six weeks. Even when they do see patients with severe hypertension, their options for initiating or increasing therapy are not always clear.

[Slide.]

Some treatments have problems with side effects. Others, like efficacy, and for many regimens the optimal dosing and titration is

unclear.

Starting with monotherapy, it can easily take three, four, or more titration steps to get patients on the medication they need, and what doses should be initiated, when should titration occur. Is hypotension a significant risk?

Unfortunately, there are few large, well-controlled studies in severe hypertension to answer these questions. We need a treatment with better initial efficacy, because patients with severe hypertension can go for weeks without a visit, and we need a treatment that can go to maximum dose in just one titration step instead of three or more, because titration is infrequent.

The ideal drug would provide a simple and safe regimen with an easy titration path that physicians can implement with confidence even when the opportunity for follow-up is limited.

[Slide.]

Severe hypertension is an important problem. It still affects over 2 million people in the United States. It leads to substantial

morbidity and mortality. The experience at my medical center shows that patients with severe hypertension have higher rates of emergency department visits and cardiovascular events compared to patients with mild to moderate hypertension.

Despite these clear risks, current treatment remains inadequate. We need simple therapies that can provide prompt and sustained blood pressure control with efficacy and safety that are well established.

Thank you very much.

DR. HARRINGTON: I want to open it to questions.

Bill, I have a series of issues that I want you to at least try to help me understand since, as you know, hypertension is not the primary thing I take care of in my clinical practice.

There are sort of two issues here, aren't there. There is one of getting the patient to go, and the other is how quickly do you do that. I am wondering if your data can help me understand that

better.

When you put up the figure of severe hypertension and you show the accumulation of events, what I want to really focus on is--you showed over eight years--is in the first couple of months. Do you have data from the Christiana experience that shows the accumulation of events in the very early period? I mean how risky is it to wait 42 days to have your appointment in the Christiana experience?

DR. WEINTRAUB: I don't think we have that fully analyzed yet in the Christiana experience, the little that is available to us, but if you look at the event rate, let's look at Slide 18.

[Slide.]

You will see that events accumulate rapidly over the first year, so it is a little hard for me to look at the first month, but looking at our Kaplan-Meier curves, we don't see that there is some kind of break, that you have some kind of grace period in which events don't occur.

But more importantly, I think, is the

issue of titration, because people don't titrate. We have lots of data that people don't titrate, and if they don't titrate, there is going to be risk of events that is going to start from the beginning.

Even if there aren't a massive amount in the first 42 days, in that period, there are events occurring and then they don't titrate thereafter, so that events continue to occur.

Now, these patients are not patients who are untreated. These are, in fact, patients who are being treated. These are patients who are being seen in primary care. They are already on therapy, and events are continuing to occur. So, we need a simpler path.

DR. HARRINGTON: I am going to play the role that Norm asked us to play, which is that it be more conservative than the FDA, so that will be my line of questioning that I have for you to try to understand this better.

On the slide before the Slide 17, where you put up the patient demographics, obviously the more severe hypertension patients are a different

group of patients demographically than the less severe patients.

There are more black patients. There are more patients with diabetes, et cetera. And you show the event curves or you show the components of the composite, and you note that these are unadjusted rates of events. Have you done any adjustment to try to understand the contribution actually of the hypertension specifically to the events?

DR. WEINTRAUB: Yes, we have. Can I look at Slide 63-1, please.

[Slide.]

So, here, we look at adjusted results. You will see that there is a continuing and increasing risk with more severe hypertension. In fact, we have done a Cox-Mantel analysis, of course.

DR. HARRINGTON: It is controlling for all the usual stuff.

DR. WEINTRAUB: All the usual things.

DR. HARRINGTON: Other questions? Bob, go

ahead.

DR. TEMPLE: I don't think that a whole lot of time needs to be spent showing that the worse your blood pressure is, the worse you are going to do if it doesn't get treated. I think everybody knows that.

The question here is how to label particular products to be used so that they get the desired goal better. You have been making the point, as I understand it, that if you don't get started pretty well, people don't catch up. It's not clear why they don't, but maybe the impediment to going to clinic or whatever it is, but somehow they never do, not to state the obvious. One could do that by using two drugs separately.

Do you want to say anything about why a fixed combination helps people do better than just giving a diuretic?

DR. WEINTRAUB: There are data that adherence is greater when people are taking just one pill. It is also easier for physicians. So, it's easier for physicians, it's easier for

patients. I think we have to remember the limited amount of time that physicians have with patients in the clinic which we, as physicians, feel that all the time, but the patients feel that, too.

So, we have to be able to resolve issues of how to treat patients with something like hypertension of which there are some 60-plus million patients in our society. We have to be able to resolve how we were going to do that rapidly and easily, and that is the advantage to fix those combinations.

I think years ago we all thought this was a bad idea, because we didn't understand the individual components, and that is perhaps where I was, I don't know, 20, 25 years ago. But I think many of us in practice have become much more comfortable with using fixed-dose combinations, because it is easier all around. Now, it doesn't absolve the physician for understanding the components of the fixed-dose combination and using them well.

We can take a look at Slide 63-14, which

might help a little bit. It shows how we are doing in the treatment of hypertension, looking at NHANES data from the earlier cohorts through the present, and we are still not doing well enough.

We are doing better. Maybe some of that is just fixed-dose combination, I don't know. But, even if you look at the most recent cohort, awareness of hypertension of 71 percent, under treatment 61 percent, but under control, just 34 percent. So, I think we need an easier path that allows us to get there.

DR. WARNER STEVENSON: I am hoping that we get back to this issue of adherence and compliance later this afternoon, but I was wondering, and what I would like to ask you specifically with all your experience, which expands on Bob's question, what we are doing often in identifying these patients with hypertension is identifying patients with lots of other comorbidities that predispose them to cardiovascular risk, and the degree to which we are decreasing events.

I think we need to distinguish between are

we decreasing events because we are controlling the hypertension or because it's a group of patients with metabolic syndrome, risk for cardiovascular disease, in whom therapy with angiotensin system inhibitors have other benefits that are not just reducing hypertension.

Now, when we are talking about with an angiotensin system inhibitor, that may, in fact, not really matter if we are helping people anyway. But if then we talk about the idea that controlling blood pressure where the combination is useful, if we are adding agents that may not necessarily have a benefit for the cardiovascular risks independent of the hypertension effect, say, with calcium channel blockers, then, the assumption that the combined therapy is always going to reduce events more may be different.

So, I guess my question is, to what extent do you think the event reduction is related to our reducing hypertension versus the fact that we have addressed a high-risk population, such as in the HOPE trial in whom addition of a renin-angiotensin

system inhibitor would be beneficial regardless of the hypertension?

DR. WEINTRAUB: It is a very interesting question and an important point. Obviously, I think everyone here believes in treating all the risk factors and risk factor control.

I, for instance, chaired a CDC Working Group on the poly pill. I am not a full believer in it. I think it needs to be tested. But, with the poly pill, we could potentially have a combination agent with six agents all together. This needs to be investigated in clinical trials, and Nick Wald, who originally pushed the poly pill, suggested that we could have an event rate reduction of 80 percent. That may be a little bit fanciful, but it is intriguing and worth testing.

So, I think all of us believe in controlling all of the modifiable risk factors. There is excellent clinical-trial data, just exquisite clinical trial data, to tell us that that is a worthwhile thing to do.

Now, hypertension, in particular, as Dr.

Giles pointed out, virtually, every study that has looked at blood pressure reduction, no matter what the agent, has shown a reduction in events. I think it is almost impossible to argue with the idea that lowering blood pressure would not prevent events. The clinical-trial data are just exquisite and there are lots and lots and lots of trials with lots and lots of different agents.

DR. TEMPLE: Do you have any comment on the question of whether severe is the right dividing line? The company has proposed--and I understand the simplicity of it, if it's severe, hit them with two--actually, the last slide in the total presentation shows depending on what your goal is, there are people who aren't severe who won't be very likely to get to goal if you don't use two drugs, too.

Do you have a view about that? You know, a diabetic with a blood pressure of only 160.

DR. WEINTRAUB: I am speaking totally for myself here. My own feeling as a clinician and clinical investigator, outcomes research, a

clinical epidemiologist, I would be more aggressive. I think it is quite reasonable and it is consistent now with guidelines to begin people on combination therapy with a blood pressure that was in the moderate range.

I worry a little bit actually that the JNC 7 guidelines have confused things more. But, if the JNC 7 guidelines, by combining what was moderate and severe, lead us to earlier and more aggressive of both moderate and severe, then, that would be a good thing.

DR. TEMPLE: I guess the down side is it requires more thought, and there is only seven minutes.

DR. WEINTRAUB: That is the big problem.

DR. TEMPLE: We took an optimistic view I think.

DR. PAGANINI: I guess more of a general statement and then probably picking up on what Dr. Temple said.

The discussion, I think, on looking at whether or not you treat hypertension and somebody

does better when you treat it, and they don't do well is, I think, a given thing. We are rediscovering a wheel here, so let's not spend a whole bunch of time on that.

The question is what is the target population, what type of combination, picking up on what was presented earlier, what type of drugs are in this combination that may have other effects on that particular target population, what are the complication comparisons.

What are the complication comparisons for individual use in similar type dosage, or has there been any drug-drug interaction available in any type of that? What is the effectiveness of a fixed peg in a variable board? You have a fixed peg and is that fixed peg going to be forced into round holes, oblong holes, square holes, or what?

Then, finally, we are worried about are we going to use a fly swatter or a shotgun. You don't want to use a shotgun for mild. You don't want to use a fly swatter for severe. But there could be a combination of tools that you could use for

specific subpopulations.

So, with all of that sort of running around in my mind, sort of picking up on what Dr. Temple said, and what was the earlier discussions, do you see this combination of these two types of drugs, generic types of drugs--sorry for the word--but these types of drugs in a subgroup such as diabetics or CKD with proteinuria, that would be a better population even as mild to moderate hypertension?

One thing, I am sorry I am not more conservative. This might actually be a little bit more liberal.

DR. WACLAWSKI: Dr. Harrington, I would like to suggest perhaps Dr. Lapuerta could present the clinical data because I think it speaks to quite a few of the issues that Dr. Paganini has just sort of walked through the questions that he has walked through, to show the Avalide data and to show how we addressed the safety, the tolerability, the additional efficacy advantages, and then discuss a little bit further the population where

that study data might be applied.

DR. HARRINGTON: Yes, that is a very good suggestion. I think Mike has a question, though, for Bill.

DR. WEINTRAUB: Can I address Dr. Paganini just a little bit before we hear from Mike, if that's okay.

DR. HARRINGTON: Yes.

DR. WEINTRAUB: Thank you.

I agree completely with Tony, we should hear the data about the efficacy and safety of this fixed-dose combination. My feeling, in answer to your question, is there is not going to be one answer for absolutely everybody and, by having a fixed-dose combination like this, and labeling that permits early use, does not absolve physicians from thinking through the best things for every patient. It is hard to do, I think, more because of a problem of limited time with the patient than any other one thing.

You are right that we can't have a shotgun for a mild problem. We can't have a fly swatter

for a severe problem. But we need both fly swatters and shotguns, and one has to know when to use them.

I think that this fits into the mix well of various things that people need to do in treating the problem of hypertension, mild and severe.

DR. LINCOFF: I am always concerned about the idea of trying to identify subgroups of patients that would have particular benefit, because I think, in general, although sometimes they are predictive, the negative predictive value isn't very good; that is, it leaves large populations of patients you wouldn't identify that would still benefit from therapy.

So, it seems to me from the data that exists, and my question to you is, is this your impression as well, that most of the benefit is pegged to the increment of reduction.

If that is the case, and if that is really the issue we want to counter, then, as Dr. Temple has pointed out, instead of deciding based upon is

it moderate or severe by fixed guidelines of where they start, should we be leaning more toward where we need to go, because if really the only criteria that is going to predict the benefit is going to be how far we need to go, and for a given combination whatever we are talking about at the particular time we can predict that as it looks like from the data that is about to be presented, we can, for the different combinations, then, perhaps that is the way to be looking at the groups of patients rather than a criteria of moderate or severe, or both.

DR. WEINTRAUB: That is a very interesting point. It's a point that was first raised to me by Peter Sleight several years ago. He said he is more interested in risk than what the blood pressure is. It is correct as far as it goes. But, first of all, blood pressure is a very strong predictor of risk, and this is where we are right now in the clinic in treating patients.

We treat patients with Stage 1 and Stage 2, or if you prefer, mild, moderate, and severe hypertension. That is where we are and what we

really do. I think there is great data to suggest that if we lower blood pressure and we lower it well into what we would consider the normal range, the incidence of events is going to decrease.

I think that on any one day in the clinic, to say, well, we should try to total up risk and find out what the risk is, and then imply some kind of risk reduction algorithm to try and choose antihypertensive agent, it is sort of one of those things that it is a great idea. But I don't think it's where we are practicing right now.

DR. LINCOFF: What I was driving at was not a global risk factor, but simply a matter of what is the incremental reduction. It seems the risk reduction is based upon the incremental reduction of blood pressure. So, if you start at 180 or you start at 160, if you drop it 20 systolic points, you get this nearly similar risk reduction.

Is that your understanding of the epidemiologic data when the treatment data actually is really what would be more--

DR. WEINTRAUB: Yes, it is, so that would

go along the lines suggesting that there be consideration for fixed-dose combination agents like this in what had been called moderate hypertension, as well.

DR. TEMPLE: The risk reduction is based on the increment, but if you only get the systolic to 160, your risk is still pretty high, and it would be better if you got to 140.

DR. HARRINGTON: It's the end of the game, where you ultimately get.

DR. TEMPLE: The reduction appears to be as far as risk reduction roughly the same for any given decrement, but you are still high if you are high.

DR. LINCOFF: But independent of the population, if you can say this drug or this combination of drugs has X percent chance of achieving a 10/5 or 20/10 reduction, then, you can predict success depending upon where your target wants to be, where you want your target to be.

DR. TEMPLE: One kind of success, but another kind of success is whether you have gotten

to the goal, because the ultimate risk appears to relate to what your final blood pressure is, taking into account the fact that you are diabetic and have other problems.

But our thinking has been that what you are interested in is the likelihood of getting to the blood pressure you wanted to get to under JNC guidelines or anybody else, and that you can. Not surprisingly, what your starting blood pressure is tells you a lot about how likely you are to get to 130/80.

DR. HARRINGTON: Not dissimilar from the LDL story.

DR. TEMPLE: Yes, I think that's true.

DR. HARRINGTON: But that brings me just a final question for you, Bill. As we sit here thinking about if there is an analogy with the LDL story, which is a laboratory measure, very precise value, blood pressure is not the same way, and a series of questions this afternoon try to address that, questions about regression to the mean and other things.

What did you learn in the Christiana population about how good we are at measuring blood pressure? In my clinic, it is not very good, but I am wondering, across a large sample, what did you learn?

I mean you picked maximum, but you could have picked average.

DR. WEINTRAUB: That's right.

DR. HARRINGTON: Why did you do that?

DR. WEINTRAUB: Well, it is a convenient way to pick the maximum, and I think that you are right, that there are problems of regression to the mean in this classification, but all that will bias to the null. It is not going to all of a sudden pick up more events and more of an effect.

While blood pressure is a really messy thing to measure, despite that, it is an unbelievably powerful surrogate for predicting future events, and a wonderful surrogate in clinical trials.

With all the difficulties and how poorly we do at measuring blood pressure in the clinic,

and none of us are any good--I mean none of us--despite that, I think all of our evidence is that treating blood pressure decreases events.

DR. HARRINGTON: Thanks, Bill.

DR. WACLAWSKI: Dr. Lapuerta will now present the Avalide data.

Dr. Harrington, I didn't mention before, but I want to point out to the committee also that we have Dr. Stan Franklin here from the University of California at Irvine. He is an expert in hypertension, as well, as well as Dr. Weber and Dr. Berlowitz. They are available to the committee, as well, for questioning. I neglected to point that out in the introduction.

Dr. Lapuerta.

Avalide Clinical Program for Initial Treatment of Severe Hypertension

DR. LAPUERTA: Thank you, Tony.

Good morning. Dr. Weintraub spoke of the need for a simple treatment that can deliver prompt and sustained blood pressure reduction. Avalide meets this need.

The clinical program shows it to be safe and effective as initial treatment of hypertension. With 1,200 subjects, this Avalide program was large and comprehensive.

[Slide.]

The program consisted of two main studies. One is a pivotal study conducted in severe hypertension, Study 176. The other study is a supportive study in moderate hypertension, Study 185.

Supportive Study 185 provides additional safety data in a population at greater risk of hypertension and syncope. The results provide further reassurance of the safety of Avalide that is relevant to the benefit-risk assessment.

The pivotal Study 176 evaluated Avalide as initial treatment of severe hypertension. The main objectives were to evaluate the safety and efficacy of Avalide as compared to irbesartan monotherapy.

With 695 patients, it is one of the largest studies ever done in severe hypertension. To assess the safety of Avalide as initial therapy,

the study had 2:1 randomization with over 450 patients on Avalide and over 225 patient on irbesartan monotherapy.

[Slide.]

The study design included forced titration. This was done in order to examine the safety of Avalide at its maximum dose. A one-week placebo lead-in period provided an opportunity for patients to wash out any prior antihypertensive therapy.

After the placebo lead-in, patients who met the inclusion criteria were randomized 2:1 to either Avalide or irbesartan monotherapy. The initial dose of Avalide was 150 mg with 12.5 mg of hydrochlorothiazide. The initial dose of irbesartan monotherapy was 150 mg.

After one week, there was forced titration of both study arms to their maximum dose. This is a rapid one-step titration to maximum dose regardless of blood pressure in order to assess the safety of Avalide in a broad range of patients with severe hypertension.

Although the primary endpoint of the study was at Week 5, follow-up assessments continued through Week 7 in order to provide additional safety data.

[Slide.]

To make certain that the study randomized a valid population, patients had to meet both enrollment criteria and randomization criteria. The key enrollment criteria were a diastolic blood pressure greater than or equal to 110 mm of mercury in subjects who were not on current antihypertensive medication.

Those who were on monotherapy could be enrolled provided that they had a diastolic blood pressure greater than or equal to 100 mm of mercury and washed out their medication during the placebo lead-in period.

The randomization criteria required that all patients had a diastolic blood pressure greater than or equal to 110 mm of mercury at two consecutive visits during the placebo lead-in period.

The goal was to assure that all patients were truly severe, but had the potential to be controlled on monotherapy. The primary endpoints focused on diastolic blood pressure.

[Slide.]

In 176, the primary efficacy endpoint was a proportion of patients with a diastolic blood pressure less than 90 mm of mercury at Week 5.

Secondary endpoints included the proportion achieving blood pressure control to less than 140/90 at every time point, proportions of patients achieving a diastolic less than 90 at other time points, and the changes from baseline in systolic and diastolic blood pressures at every time point assessed.

[Slide.]

The safety endpoints aimed to assess overall safety, as well as specific events associated with blood pressure reduction. They included the overall frequency of adverse events, the frequency of discontinuations due to adverse events, and a collection of prespecified adverse

events of special interest.

These were chosen to be adverse events that may occur with Avalide or irbesartan monotherapy and may be of particular concern to patients with severe hypertension. They included dizziness, hypertension, syncope, headache, and potassium abnormalities.

Of note, there was no special case-report form for these events. They were special adverse events because they were prespecified, they were part of the protocol, and discussed with investigators as some of the information that we hope to glean from this study.

[Slide.]

Baseline characteristics were well balanced. The mean age was in the 50s. The population was mostly white. The baseline blood pressure was severe with diastolic blood pressures of 113 mm of mercury in both treatment arms. The systolic blood pressures were also quite elevated with blood pressures of 171 and 172.

[Slide.]

Avalide consistently lowered blood pressure further, more rapidly, and in a higher proportion of patients achieving clinically meaningful and statistically significant improvements beyond those of irbesartan for every endpoint measured.

[Slide.]

For the primary endpoint, 47 percent of patients in the Avalide arm achieved a diastolic blood pressure less than 90 at Week 5. This was compared to 33 percent of patients in the irbesartan and monotherapy arm, and the differences were highly statistically significant.

These reductions result in a higher proportion of patients achieving blood pressure control with Avalide.

[Slide.]

At every time point, a higher percentage of Avalide subjects reached blood pressures below 140/90. At the time of the primary endpoint, Week 5, Avalide controlled 35 percent of patients to 140/90, while irbesartan monotherapy controlled

about 20 percent of patients to 140/90.

There were similar significant differences at every time point. These differences arise from a consistently greater and more rapid blood pressure reduction with Avalide.

[Slide.]

The diastolic blood pressure changes were significantly greater with Avalide at every time point. The dotted line illustrates how the mean blood pressure lowering that was achieved at Week 7 on irbesartan monotherapy was already achieved several weeks earlier on Avalide. More importantly, the difference between treatment arms was almost 5 mm in diastolic blood pressure, a clinically meaningful difference.

Results for systolic blood pressure followed the same pattern.

[Slide.]

There was statistically significantly more blood pressure lowering with Avalide than irbesartan monotherapy at every time point assessed. The same type of dotted line shows that

the blood pressure reductions achieved at Week 7 on irbesartan monotherapy were achieved several weeks earlier with Avalide. Moreover, the difference again was clinically meaningful, almost 10 mm of systolic blood pressure.

Since the data were robust and statistically significant for every endpoint, at every time point, post-hoc efficacy analyses were conducted.

[Slide.]

These included an examination of how blood pressures were broadly distributed at the time of the primary endpoint. Every subject started with severe hypertension, so at baseline, essentially, 100 percent of the blood pressures were in the severe category at the right-hand side of the graph.

After five weeks on irbesartan monotherapy, there was a broad shift towards lower blood pressure levels with many people ending up with moderate levels, some with mild levels, and a few achieving blood pressure control to less than

140/90. But with greater efficacy, Avalide treatment resulted in a greater shift in blood pressure distributions.

The most immediate goal of therapy is to avoid severe blood pressure elevation. Ninety-five percent of Avalide subjects were no longer severe at Week 5. This left only about 5 percent severe on Avalide, while approximately 14 percent of irbesartan monotherapies had severe blood pressure values at Week 5. The difference was statistically significant.

Moderate hypertension still puts patients at substantial cardiovascular risk and there were statistically significant and meaningful differences in the presence of moderate blood pressure levels at Week 5. About 30 percent of irbesartan subjects had moderate blood pressure levels at Week 5 compared to 16 percent of Avalide patients.

JNC 7 guidelines refer more broadly to Stage 2 hypertension, merging moderate and severe categories.

At the time of the primary endpoint, 44 percent of subjects on irbesartan had Stage 2 blood pressure levels compared to 21 percent of subjects on Avalide.

[Slide.]

While the study was not designed for subgroup analyses, there were some relevant results. Severe hypertension disproportionately affects African-Americans. Although African-Americans respond less well to agents acting on the renin-angiotensin system, their response to combination therapy is similar to that of whites, so the relative benefit of Avalide compared to irbesartan monotherapy was even greater in African-Americans.

African-Americans have a target blood pressure goal of 130/80 mm of mercury.

[Slide.]

In Study 176, no diabetic achieved a blood pressure less than 130/80 on irbesartan monotherapy. Avalide lowered blood pressure substantially in diabetics, and many achieved a

blood pressure of less than 140/90, but since their target is diastolic less than 80, these patients required diastolic lowering of over 30 mm of mercury.

Avalide lowered diastolic blood pressure by 24 mm of mercury, which is good efficacy, but patients with severe hypertension and diabetes will need even a third medication. A goal of 130/80 is simply very far away. The further away a patient is from goal, the more likely a combination of drugs will be necessary. This was evident in Study 176.

[Slide.]

The chart on the left represents the probability of achieving a systolic blood pressure target of 140 mm of mercury with Avalide or irbesartan monotherapy. The curves are based on logistic regression. The separation of the curves reflects the greater proportion of patients on Avalide who achieved goal regardless of their baseline blood pressure.

Avalide lowers systolic blood pressure

substantially, 31 mm of mercury, but patients with systolic blood pressures of 180, 190, or 200 are already 40, 50, or 60 mm away from their goal, so many will need even a third medication.

The pattern for diastolic blood pressure is the same. Patients with higher diastolic blood pressures are more likely to require two medications to achieve their blood pressure targets.

Those with diastolic blood pressures of 120 or more are very likely to need even a third medication.

[Slide.]

Better efficacy with initial use of Avalide meant that more patients achieved a blood pressure of less than 90 mm of mercury, and more patients achieved blood pressure control to less than 140/90.

These advantages resulted for more rapid and more effective blood pressure reductions of systolic and diastolic blood pressure. The difference in efficacy was approximately 10 mm

systolic and 5 mm diastolic, which is clinically meaningful.

For people with severe hypertension, these greater reductions are especially relevant in terms of their exposure to severe blood pressure levels.

These efficacy results are different from those obtained in the registrational program conducted for Hyzaar.

[Slide.]

Hyzaar is the combination of losartan and hydrochlorothiazide. It is approved for initial treatment of severe hypertension based on a pivotal study with a similar design.

In both Study 176 and the Hyzaar study, initial combination treatment was compared to the angiotensin receptor blocker as monotherapy. The blood pressure criteria for randomization were the same. Of note, randomization criteria had to be admit twice in both studies to ensure the population was truly severe.

Baseline blood pressures were essentially identical. Study 176 had 100 percent titration and

the Hyzaar study had almost 90 percent titration to the maximum dose.

An important difference between the studies relates to the number of prior medications allowed. In Study 176, 50 percent of patients were not on prior medication, and those who were on prior medication were only on monotherapy, one drug.

Results in the naive and previously treated population were the same in Study 176 in terms of efficacy and safety. Study 176 is therefore reflective of initial treatment of severe hypertension. However, in the Hyzaar study, patients were on an average of two medications when they enrolled. This is not quite the setting of initial treatment.

When patients are not controlled on two or three medications, they are unlikely to achieve control when these medications are discontinued and they are randomized to potentially only one. This difference in study design may explain the differences in study results.

[Slide.]

As Dr. Waclawski mentioned, control rates in Study 176 were higher than previously shown in the Hyzaar program. This difference was associated with a very large difference in mean blood pressure reductions. Avalide in Study 176 lowered blood pressure 10 mm of mercury more than Hyzaar in its pivotal study.

Now, irbesartan and losartan as monotherapies have been compared in head-to-head clinical trials. Irbesartan has lowered diastolic blood pressure more by 1 to 4 mm. This larger difference in blood pressure between the two studies is more likely reflective of differences in study design.

What is the meaning of this difference? It provides, in Study 176, an opportunity to evaluate whether aggressive use of an effective combination treatment is still safe. In Study 176, a large, 31 mm reduction in blood pressure was observed in just five weeks.

[Slide.]

Results of Study 176 provide important reassurance about safety.

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The blood pressure reductions of Avalide were obtained without any increase in adverse events. Importantly, there were no substantive increases in dizziness, hypotension, or syncope.

The safety of Avalide was consistent with the established tolerability and safety of Avalide in its current indication. Avalide was safe and well tolerated. Patients treated with Avalide had a 29.9 percent adverse event rate, and patients treated with irbesartan monotherapy had a 36.1 percent overall adverse event rate.

Serious adverse events were uncommon. None of the serious adverse events were related to treatment in this study. Although it was not reported by the investigator as a serious adverse event, there was a transient ischemic attack in a subject taking Avalide. The patient reported it in clinic two days after the event resolved. She was not hospitalized, and it was considered unrelated

to study therapy. But transient ischemic attacks are serious, and if counted among the serious adverse events, then, the incidences on Avalide and irbesartan are both 0.4 percent.

Discontinuations due to adverse events were few. There was a discontinuation that was not listed as due to an adverse event, yet, the subject did have a headache. If this case is counted, then, the incidences of discontinuations due to adverse events are 2.1 percent on Avalide and 2.2 percent on irbesartan. There were no deaths.

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Importantly, adverse events of special interest were also similar between treatment groups. They occurred in 9 percent of Avalide patients and 11 percent of subjects on irbesartan monotherapy.

In particular, there was no increase in dizziness with initial use of Avalide. Headache was less common. Here, hyperkalemia and hypokalemia are reported as adverse events according to the judgment of the investigator, not according to

formal laboratory criteria.

Marked laboratory abnormalities for potassium were formally defined in this study, as a potassium less than 3 or a potassium greater than 6. There were no potassium values less than 3 in the study, but potassium values greater than 6 did occur in 0.6 percent of Avalide subjects and 1.3 percent of irbesartan subjects.

Hypotension was uncommon and consistent with current labeling with Avalide, which describes an incidence of hypotension of 1 percent. Here, with the initial use of Avalide in severe hypertension, the observed incidence was 0.6 percent. This was a total of three cases, two reported as mild and one as moderate.

There was no syncope in either treatment arm.

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Every case of hypotension had a systolic blood pressure of at least 130 mm of mercury at every clinic visit. Diastolic blood pressures were between 78 and 96 in the clinic. None of the

patients had hypotension on the starting dose. None of the patients had orthostatic changes on standing. All of these cases resolved.

Of note, these are only clinic blood pressures. Blood pressures are not available at the exact moment that hypotension occurred in the three subjects who reported symptoms.

[Slide.]

Treatment-related adverse events occurred with similar frequency between treatment arms. The most common treatment-related adverse event was dizziness and headache. Neither of these was more common with Avalide than irbesartan monotherapy.

[Slide.]

The rate of discontinuations was also similar across treatment arms. About 10 percent of subjects discontinued. Very few subjects discontinued due to adverse events.

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To better understand the potential for hypotension and dizziness, a separate analysis was performed. This was done on subjects who had at

least one low systolic or diastolic measurement at any point in treatment.

There were 9 such subjects, all on Avalide, who had at least one systolic blood pressure less than 110 mm of mercury during the study. They were all less than 65 years of age. None of them had a systolic blood pressure less than 110 mm of mercury on the initial dose of Avalide.

Six of the 9 had blood pressures less than 140/90 at Week 1. So, in actual practice, they would not have been titrated to the maximum dose of Avalide.

Three of the subjects reported dizziness, which was mild in 2 and moderate in 1.

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Of there 9 subjects, 1 also had a single diastolic blood pressure less than 60. He was the only subject with a diastolic blood pressure less than 60 in the entire study. He was treated with Avalide, representing 0.2 percent of Avalide subjects. He had a blood pressure less than 140/90

at Week 1 and therefore may not have been titrated to the maximum dose of Avalide in actual practice. His only diastolic blood pressure below 60 was recorded at Week 7. He had no adverse events and completed the study without incident.

These analyses revealed that no subject 65 or older had a low measurement of either systolic or diastolic blood pressure, but it is important to consider safety in this older population.

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There were 92 patients 65 years and older on Avalide in Study 176. They tolerated Avalide well, without any hypotension or syncope. Dizziness in Avalide was not more common in those 65 and older than in those less than 65 years of age. Overall adverse events were not more common in patients 65 and older.

Across the entire population studied, Avalide was safe and well tolerated.

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Initial use of Avalide in severe hypertension showed similar safety to irbesartan

monotherapy without any increase in dizziness, without hypotension being uncommon and occurring at a rate consistent with the current product label, with no syncope, and with good tolerability in subjects 65 and older.

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Study 185 provides important data to support the use of Avalide in severe hypertension.

[Slide.]

Much of the support comes in terms of safety information. Study 185 also provides relevant efficacy data. If the blood pressure lowering of Avalide is not too much to tolerate for patients with moderate hypertension, then, it is not too much to tolerate for patients with severe hypertension.

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The study design also provides important information on the relative contributions of the individual components of Avalide as there were two monotherapy arms, hydrochlorothiazide monotherapy and irbesartan monotherapy.

Patients with moderate hypertension--and that is a systolic blood pressure between 160 and 179 or a diastolic blood pressure between 100 and 109--were randomized after a placebo lead-in period.

Randomization was to either of three treatment arms. The randomization, however, was in a 3:1:1 ratio again with more patients being randomized to Avalide in order to provide more comprehensive safety data.

The dose of Avalide for the moderate subjects in Study 185 was the same dose used in Study 176, a starting dose of 150 mg of irbesartan with 12.5 mg of hydrochlorothiazide.

The starting dose in the hydrochlorothiazide monotherapy arm was 12.5 mg, and the starting dose in the irbesartan monotherapy arm was 150 mg.

After a period of two weeks, the medication was titrated to maximum dose in all treatment arms. As in Study 176, this forced titration was done without regard to blood

pressure. It was conducted in order to examine the safety of the maximum dose.

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Here, the primary endpoint was at Week 8. The primary efficacy endpoint was the change from baseline in systolic blood pressure. Secondary efficacy endpoints covered other blood pressure parameters including diastolic blood pressure change at Week 8 and 12, systolic blood pressure change at Week 12, and the proportion of patients achieving a blood pressure less than 140/90 between treatments, at Weeks 8 and 12.

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The safety endpoints in Study 176 were the same as the safety endpoints in Study 185--I meant that vice versa. Study 185 had the same endpoints as 176. The safety endpoints included the frequency of adverse events, discontinuations due to adverse events, and the same collection of adverse events of special interest. However, patients were followed to Week 12 in Study 185, providing a longer period of assessments, enabling

the collection of a higher number of events.

With the exception of the lower blood pressures, the demographics in Study 185 were similar to the demographics in Study 176.

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Baseline blood pressures were in the moderate range with a systolic blood pressure of over 160. Some of the patients were randomized on systolic criteria alone, having an isolated systolic hypertension. So, the mean diastolic blood pressure of 98 here reflects a mix of values, some in the moderate range and some that were lower. As in 176, Avalide reduced blood pressure substantially more than either monotherapy.

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At Week 8, Avalide reduced mean systolic blood pressure significantly more than either monotherapy. The 27 mm change from baseline here is similar to the 31 mm change from baseline seen in Study 176.

Irbesartan monotherapy achieved a greater numeric reduction in mean systolic blood pressure

than hydrochlorothiazide. The confidence intervals between the two treatments, irbesartan monotherapy and hydrochlorothiazide monotherapy, do not overlap. These results support the choice of irbesartan as a comparison to Avalide in Study 176.

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Changes in systolic blood pressure were consistently greater for Avalide and were statistically significant at every time point. The pattern is repeated for diastolic blood pressure.

[Slide.]

Avalide showed superior blood pressure reductions at every time point as in Study 176.

[Slide.]

These efficacy results were as expected in this population. More importantly, initial use of Avalide was safe and well tolerated even when force titrated to maximum dose in a moderately hypertensive population.

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Adverse events were very similar between Avalide and irbesartan monotherapy and generally

consistent with those of Study 176. There were fewer adverse events on hydrochlorothiazide monotherapy. Low doses of 12.5 mg and 25 mg of hydrochlorothiazide were very well tolerated.

Treatment-related adverse events were also similar between Avalide and irbesartan monotherapy, and lower on hydrochlorothiazide monotherapy. Serious adverse events were uncommon and none were related to study therapy except for one, which will be described in further detail shortly.

Discontinuations due to adverse events were 2 percent greater with Avalide than either monotherapy. This was due to approximately 2 percent of Avalide patients who did not tolerate its maximum dose, and this will be discussed further shortly.

There were no deaths in the study.

There was one serious adverse event deemed by the investigator as probably related to therapy.

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The case involved a 50-year-old woman who had atypical chest pain and presented to the

emergency room. She had an electrocardiogram which was normal. Nevertheless, she was admitted to rule out myocardial infarction. She had a coronary catheterization and her coronary arteries were normal.

The only abnormality found during the entire hospitalization was a potassium value of 3.2 mEq/L. This was mild hypokalemia and may not explain her chest pain, yet it was the only abnormality identified, and the physician described this case as symptomatic hypokalemia and assigned the relationship to study drug as probable.

[Slide.]

In this moderate hypertension population, the incidence of adverse events of special interest was similar to that seen in pivotal Study 176. Adverse events of special interest occurred with a frequency of about 11 percent on Avalide and 7 percent in the monotherapy arms.

Dizziness was not more common with Avalide than irbesartan monotherapy, but it was less frequent on hydrochlorothiazide monotherapy.

The incidence of hypotension was less than 1 percent on Avalide despite the forced titration to highest dose in this moderate population. This is consistent with the results of Study 176.

There was no syncope on Avalide. There was one case of syncope on a subject taking hydrochlorothiazide. It was not related to the medication.

[Slide.]

Total discontinuations were very similar across treatment arms. They were 12 and 11 percent in the different treatment arms. Discontinuations due to adverse events were 2 percent higher on Avalide. This was due to dizziness or hypotension on the maximum dose.

In examining these cases, the majority had blood pressures less than 140/90 on the starting dose of Avalide. They were only titrated to the maximum dose because of the protocol requirement.

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Even with forced titration in the moderate population, Avalide was safe and well tolerated in

elderly subjects. There was no hypotension or syncope in Avalide in subjects 65 and older, nor was there any increase in dizziness or any increase in overall adverse events in this population.

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In Study 185, initial use of Avalide had good overall safety and efficacy. Patients with moderate hypertension tolerated initial use and forced titration of Avalide with a similar incidence of adverse events to irbesartan monotherapy.

The incidences of dizziness and hypotension were low and consistent with the current product label. Two percent of patients with moderate hypotension did discontinue Avalide due to dizziness or hypotension, largely because the protocol required forced titration to the maximum dose.

There was no syncope on Avalide and tolerability was good in subjects 65 years of age and older.

These results are supportive of the safety

shown in Study 176. The superior efficacy of Avalide in this registrational program is consistent with that of the original NDA.

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The original hypertension program evaluated a range of doses of irbesartan monotherapy, hydrochlorothiazide monotherapy, and combinations of the two.

From left to right is a range of hydrochlorothiazide doses going from zero to 25 mg. From back to front is a range of irbesartan doses going from zero to 300 mg. So, the steep yellow bar shown with the greatest efficacy is Avalide at its maximum dose, the two individual components working together.

[Slide.]

This study further established the potential for Avalide to reduce potassium abnormalities. At its 25 mg dose, hydrochlorothiazide reduced potassium by 0.3 mEq/L. That is shown by the long yellow bar in the back.

At its 300 mg dose irbesartan raised