FOOD AND DRUG ADMINISTRATION

NINETY-SEVENTH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUG ADVISORY COMMITTEE

8:01 a.m.

Friday, July 19, 2002

Versailles Ballroom
Holiday Inn - Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

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ATTENDEES (Continued)

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ELLIOTT LEVY, M.D.
MILTON PACKER, M.D.
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ANTHONY WACLAWSKI, PH.D.

C O N T E N T S

NDA 21-188, Vanlev (omapatrilat)
Bristol-Myers Squibb Company,
Proposed for the Treatment of Hypertension

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P R O C E E D I N G S

(8:01 a.m.)

DR. BORER: It's not quite 8:01, so everybody has had some extra time. We'll begin this morning's session which is consideration of NDA 21-188, Vanlev, sponsored by Bristol-Myers Squibb.

The committee is slightly restructured today because of conflict of two members. So, we'll introduce the active members, including our nonvoting member guest. Before we do that, let me ask you please to turn off your cell phones, if they happen to be on.

Why don't we start on this side. Tom.

DR. PICKERING: I'm Tom Pickering from the Cardiovascular Institute at Mount Sinai Medical Center in New York.

DR. CUNNINGHAM: I'm Susanna Cunningham from the University of Washington in Seattle.

DR. CARABELLO: I'm Blase Carabello from the Houston VA and from the Baylor College of Medicine.

DR. NISSEN: Steve Nissen with the Cleveland Clinic School of Medicine.

DR. ARMSTRONG: Paul Armstrong from the University of Alberta.

DR. BORER: I'm Jeff Borer, Weill Medical College at Cornell University in New York City.

MS. PETERSON: I'm Jayne Peterson. I'm the

DR. FLEMING: Tom Fleming, University of acting Executive Secretary of the Advisory Committee. Washington, Seattle.

DR. THROCKMORTON: Doug Throckmorton. I'm the Director of the Cardio-Renal Division in the FDA.

DR. BORER: We'll have our additional member introduce himself when he comes in.

Jayne, will you please present the conflict of interest statement?

MS. PETERSON: Thank you.

The following announcement addresses conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting 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 which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Dr. Jeffrey Borer has been granted a waiver under 18 U.S.C. 208(b)(3) for his potential consulting for the sponsor on a competitor to Vanlev on unrelated matters.

Potentially he could receive less than $10,001 a year.

Dr. Susanna Cunningham has been granted waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4), amendment of section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in a competitor to Vanlev. The stock is valued between $25,000 and $50,000.

Dr. Thomas Fleming has been granted a waiver under 18 U.S.C. 208(b)(3) for his participation on two data safety monitoring committees for a competitor and the parent of a competitor to Vanlev on unrelated matters. He receives less than $10,000 per year for each activity.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

We would also like to disclose for the record, because of her reported interest, Dr. Beverly Lorell, a committee member, is excluded from participating in all official matters concerning new drug application 21-188, Vanlev, omapatrilat, sponsored by Bristol-Myers Squibb proposed for the treatment of hypertension.

With respect to FDA's invited guest, Dr. Pickering has a reported interest that we believe should be made public to allow the participants to objectively

evaluate his comments. Dr. Pickering is listed as a Vanlev consultant for Bristol-Myers Squibb and was paid in 2001. He has received a research grant from Bristol-Myers Squibb in 2001 for analyzing their data on 24-hour blood pressure. He has done nothing for the company in 2002.

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 such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask 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. Borer.

DR. BORER: Mike, will you introduce yourself to the company?

DR. ARTMAN: I'm Mike Artman. I'm at New York University School of Medicine.

And I would just like the record to show that Dr. Borer's clock, according to the U.S. atomic clock, is about 3 minutes fast. Thank you.

(Laughter.)

DR. BORER: Well, it means we get through 3

minutes earlier.

Let's begin the sponsor's presentation then, if we can. Dr. Waclawski.

DR. WACLAWSKI: Thank you, Dr. Borer. Good morning to you, members of the advisory committee, FDA, ladies and gentlemen.

I'm Anthony Waclawski with the Regulatory Sciences Group at Bristol-Myers Squibb. It's my pleasure to take a few minutes today and introduce our presentation.

The purpose of our presentation today is to discuss the data that is relevant to the use of omapatrilat in hypertension, specifically in patients with hypertension that is difficult to control with other agents.

Omapatrilat is a vasopeptide ACE inhibitor. It is the first agent in this new class of antihypertensive agents to be discussed by this committee.

As background, I will briefly review the regulatory history of the application and then give you an overview of this morning's presentation.

The original NDA was filed in December of 1999. This NDA was based on an extensive preclinical and clinical development program. The clinical studies were mainly conducted as placebo-controlled or active-controlled, forced-titration studies.

In April of 2000, Bristol-Myers Squibb withdrew

the NDA. This was in response to questions raised by the FDA regarding the comparative incidence and severity of angioedema with omapatrilat compared to existing agents.

In August of 2000, the 6-month, 25,000-patient OCTAVE study was initiated. OCTAVE stands for omapatrilat cardiovascular treatment assessment versus enalapril. This study was conducted to more clearly define the efficacy and safety of omapatrilat compared to the ACE inhibitor enalapril.

In December of 2001, based upon the review and analysis of the results of the OCTAVE study, the NDA for omapatrilat for the treatment of hypertension was resubmitted. The resubmitted NDA included data from approximately 19,000 subjects treated with omapatrilat, making it several times larger than recent NDAs submitted for hypertension. The size and scope of the omapatrilat NDA allowed for the characterization of the safety and efficacy of omapatrilat in a broad range of patients.

In addition, although not part of the NDA for hypertension, omapatrilat has been studied in an extensive heart failure program, including the recently completed OVERTURE study. There's a question today about OVERTURE and its implications for hypertension on the list of questions today.

With that background, I will now provide an

overview of our presentation.

First, in terms of efficacy, data will be presented to demonstrate that omapatrilat is an effective antihypertensive agent, more effective as monotherapy than lisinopril, losartan, or amlodipine. In addition, data from the OCTAVE study will be presented. These data demonstrate that an omapatrilat-based regimen is more effective than an enalapril-based regimen in a broad range of patients under conditions that closely mimic clinical practice.

In terms of safety, data from the OCTAVE study will be presented that demonstrate that patients treated with omapatrilat experience angioedema about three times more frequently than those patients treated with enalapril. In OCTAVE, life-threatening angioedema occurred in patients treated with omapatrilat at a rate of approximately 2 per 12,000 patients. In OCTAVE, no patients treated with enalapril experienced life-threatening angioedema.

In terms of benefit and risk, these data, taken together, present difficult and complex questions about benefit and risk. How should one evaluate a compound that may offer superior benefit when it also carries an increased risk of a potentially life-threatening adverse event? How should the expected benefit be estimated? What level of risk is acceptable? And in what patients is

perhaps the benefit-to-risk favorable? Data will be presented today to help address these issues.

Let me tell you about the approach that we have taken.

Since the filing of our NDA in December of last year, we have performed numerous additional statistical analyses of the OCTAVE data and have had extensive consultations with medical and regulatory experts and the FDA aimed at helping us to answer these questions.

In light of the risk of angioedema, we have looked for ways to maximize the benefit and minimize the risk. Maximizing the benefit means to target the use of omapatrilat to those patients that are most likely to benefit from therapy. These patients would have an increased cardiovascular risk and would have hypertension that is difficult to control with available therapies. Data will be presented today which demonstrate that omapatrilat provides substantial blood pressure reductions in these patients.

Regarding the management of risk, we have initiated discussions with the FDA about how to manage the risk of angioedema. We have thus far focused on the identification of the risk factors of angioedema and on the use of patient education about angioedema to help minimize the risk of severe outcomes.

You have in your briefing book an FDA review of our proposed risk management plan. The review points out that risk management will not likely reduce the risk of angioedema with omapatrilat to that of an ACE inhibitor. We agree with this, and this is not the objective of the plan. Rather, the objective is to minimize the risk of life-threatening angioedema using education. The review acknowledges that this might be possible, and we are continuing to work with FDA on this plan. We are confident that if omapatrilat is approved on the basis of the clinical data, that we can find a mutually acceptable plan with the FDA.

I will now come back to the target population and be a little bit more specific since our presentation today is focused on these patients.

We'll present data that supports the use of omapatrilat in patients that can be described with two broad criteria. These patients will have comorbid conditions or characteristics associated with high cardiovascular risk, such as a history of cardiovascular disease, patients with target organ damage, those with three or more cardiac risk factors, or patients with diabetes or renal disease. They would also have hypertension that is difficult to control with existing agents.

As you'll see from our presentation today, black patients and patients who smoke are at a higher risk of angioedema. Use of omapatrilat in these patients must be accompanied by particular caution.

This is the target population. We will present data today that supports the use of omapatrilat in these patients. When evaluating these data, we recognize that the advisory committee and the FDA will rely upon their scientific judgment when considering how these data may support a recommendation for the approval of omapatrilat. We've been working through these issues for some time and are looking forward to your deliberations.

Bristol-Myers Squibb has invited several consultants to the meeting today. They are Drs. Black, Hennekens, Kaplan, Packer, Neaton, and Weber. These experts are here to facilitate the advisory committee discussions and deliberations.

Finally, the agenda for the presentation is as follows. Dr. Levy, who leads the clinical development program for omapatrilat at Bristol-Myers Squibb, will present the clinical efficacy data. Dr. Kaplan, from the University of South Carolina, an expert in angioedema and a member of the OCTAVE angioedema endpoint adjudication committee, will provide a short background on this event. Dr. Levy will then return to present the safety data and

the benefit-risk summary.

I should note that although Dr. Hennekens was listed on the agenda that may be in your briefing package, he will not make a presentation today on risk-benefit, but he is here to answer any questions.

There is also a question about OVERTURE. We have asked Dr. Packer to come and make a short presentation about OVERTURE. This is also a small change from your agenda.

Dr. Black will follow Dr. Packer and he will provide a clinician's perspective. I will then return and conclude our presentation.

That ends the introduction. I would now like to introduce Dr. Elliott Levy who will present the clinical efficacy data.

DR. LEVY: Dr. Borer and members of the committee, thank you for your attention. My name is Elliott Levy, and I lead the omapatrilat clinical development team.

Before discussing the efficacy of omapatrilat, I'd like to reemphasize a point made by Dr. Waclawski in his introduction. Bristol-Myers Squibb is asking the advisory committee to consider omapatrilat for use in patients who have established cardiovascular disease or other characteristics associated with similarly high

cardiovascular risk and whose blood pressure is difficult to control with existing therapies. In this population, the benefit of omapatrilat treatment strongly outweighs the risk of angioedema.

I'll present efficacy data this morning in the following order. In four placebo-controlled trials, including approximately 2,400 subjects, omapatrilat was shown to reduce systolic and diastolic blood pressure in dose-dependent fashion.

In six active-controlled trials involving approximately 2,700 subjects, the maximum intended dose of omapatrilat, 80 milligrams, was shown to reduce blood pressure more effectively than the maximum labeled dose of the widely used antihypertensives lisinopril, amlodipine, and losartan.

In OCTAVE, which included about 2,500 subjects, an omapatrilat-based regimen was shown to reduce blood pressure more effectively than one based on enalapril. Omapatrilat was also shown to reduce blood pressure effectively in the proposed target population: patients with high cardiovascular risk and difficult-to-control hypertension.

In four placebo-controlled, randomized, double-blind, dose-ranging studies, omapatrilat at doses of 10 to 80 milligrams was shown to reduce systolic and diastolic

blood pressure in dose-dependent fashion. At the proposed starting dose of 10 milligrams, omapatrilat produced statistically significant reductions in blood pressure relative to placebo. At the maximum intended dose of 80 milligrams, omapatrilat reduced systolic blood pressure by about 16 millimeters of mercury relative to placebo and 19 millimeters of mercury overall.

These changes in blood pressure were substantially larger than those historically reported with existing agents, and based on these findings a series of six active-controlled, randomized, double-blind trials were performed in which omapatrilat 80 milligrams was directly compared to the maximal recommended dose for the widely used antihypertensive agents amlodipine, lisinopril, and losartan. For clarity, I'll present the systolic blood pressure results in these studies. The results for diastolic blood pressure were similar.

In three of these studies presented here, efficacy was assessed by measurement of seated blood pressure in the physician's office using standard cuff methodology at the time of trough blood levels, so about 24 hours after administration of the previous dose. Omapatrilat produced statistically significant reductions in blood pressure relative to amlodipine, lisinopril, and losartan, ranging from 3 millimeters of mercury systolic

relative to amlodipine on the left-hand side, and moving right, 5 millimeters of mercury relative to lisinopril, and 7 millimeters of mercury relative to losartan.

You may have noted that in one of these studies conducted versus lisinopril, reductions in blood pressure were smaller than observed elsewhere. This study was performed in African Americans in whom the response to drugs that inhibit the renin-angiotensin system is known to be diminished. As expected, the response to both omapatrilat and lisinopril was reduced in this study, but systolic blood pressure was reduced about 5 millimeters of mercury more with omapatrilat than with lisinopril.

In three other studies displayed here, efficacy was assessed by ambulatory blood pressure monitoring. Ambulatory blood pressure has been shown to correlate more closely with target organ damage than does office blood pressure. And ambulatory blood pressure also captures the effect of drug on blood pressure over 24 hours during normal daily activities, rather than at a single time point in the physician's office.

In these studies, omapatrilat was also shown to reduce blood pressure more effectively than maximal recommended doses of amlodipine, lisinopril, or losartan. Here the differences ranged from about 5 to 6 millimeters of mercury relative to amlodipine to about 7 millimeters of

mercury relative to lisinopril and 8 to 9 millimeters of mercury relative to losartan. These differences between omapatrilat and comparator were somewhat greater than observed in the office blood pressure studies previously presented, which is the opposite of what one might expect since ambulatory pressures tend to be lower than office blood pressures and to vary over a smaller range.

The course of blood pressure reduction over 24 hours is illustrated in this representative tracing from the amlodipine comparison study. At every time point over 24 hours, omapatrilat reduced blood pressure more than amlodipine, as illustrated by the bottom curves. Similar results were observed in ambulatory blood pressure trials conducted versus lisinopril and losartan.

In sum, in these active-controlled trials, omapatrilat at 80 milligrams produced greater reductions in blood pressure than the maximum recommended doses of amlodipine, lisinopril, and losartan. A major objective of OCTAVE was to determined whether omapatrilat would be superior to another agent in conditions similar to those encountered in clinical practice where an antihypertensive therapy is titrated electively to reach blood pressure target and supplemented by other agents as needed.

OCTAVE used a simple protocol of a large sample size and few exclusion criteria so that the efficacy and

safety of omapatrilat could be assessed in a variety of demographic and clinical subgroups.

In OCTAVE, 25,000 hypertensive patients were randomized in equal number to treatment with omapatrilat beginning at 10 milligrams or enalapril beginning at 5 milligrams. After an initial fourth titration step at week 2, physicians were instructed to titrate patients as needed to reach blood pressure target at weeks 4 and 6. At week 8, the end of the study drug titration phase, the dose of study medication was fixed, and investigators were instructed to add other antihypertensive agents as needed in order to reach blood pressure target at weeks 8 and 16. The dose range selected for omapatrilat reflected the intended clinical dose range, while the enalapril dose regimen was selected in accordance with the label and customary clinical practice.

For assessment of efficacy, subjects were assigned at randomization to one of three prespecified study groups, each representing a potential manner of use of omapatrilat. Patients not receiving antihypertensive therapy at enrollment, about 9,000 patients, were assigned to study group 1 and received omapatrilat or enalapril as initial therapy for hypertension.

Patients receiving antihypertensive therapy at enrollment but not controlled were assigned to study groups

2 or 3. Those with mildly elevated blood pressure, systolic blood pressures of 140 to 159, or diastolics of 90 to 99, were assigned to study group 2 and received omapatrilat or enalapril as replacement for existing therapies, all of which were discontinued at randomization. About 11,000 patients were assigned to this group.

Study group 3 patients included those with more markedly uncontrolled blood pressure at randomization, systolic blood pressure of 160 to 179 or diastolic pressure of 100 to 109, and whose baseline regimen did not include an ACE inhibitor. These patients received omapatrilat or enalapril in addition to existing therapies which were continued beyond randomization. About 5,000 patients were assigned to this study group.

Two efficacy objectives were specified as co-primary study endpoints. The first, change in systolic blood pressure from baseline to week 8, reflected the effect of study drug on blood pressure, titrated electively as needed to reach target. The second co-primary efficacy objective, the use of new adjunctive antihypertensive therapy between weeks 8 and 24, reflected the extent to which a more effective monotherapy might reduce the need for additional antihypertensive therapy.

Important safety objectives included the assessment of the incidence of adverse events, as well as

the incidence and severity of angioedema. These will be discussed in more detail in the safety portion of the talk.

The study results at week 8, the end of the study drug titration period, are summarized here. If omapatrilat had greater inherent efficacy, then one might expect that subjects randomized to enalapril would be more likely to be titrated upward in order to reach blood pressure target than subjects randomized to omapatrilat, and this in fact was observed. As shown on the right-hand panel of this slide, subjects randomized to enalapril were more likely to be titrated to top dose of study drug than subjects randomized to omapatrilat, and this was true whether study drug was used as initial therapy for hypertension in study group 1, as replacement for existing therapy in study group 2, or in addition to existing therapy as in study group 3.

Between 33 and 52 percent of patients randomized to enalapril were titrated to 40 milligrams, the maximal dose. This pattern of therapy with robust doses of enalapril is considerably more aggressive than that encountered in clinical practice. Despite greater use of maximal study therapy in patients randomized to enalapril, those randomized to omapatrilat had greater reductions in systolic blood pressure at week 8, as shown in the left-hand panel. The difference in systolic blood pressure

reduction of about 3 to 4 millimeters of mercury was highly consistent whether patients received study drug as initial therapy, as replacement, or add-on therapy.

You might note that the blood pressure reductions with both study drugs were smaller in group 2 than in groups 1 and 3 because group 2 subjects discontinued all prior antihypertensive therapy at enrollment. Their blood pressure changes reflect both the antihypertensive effect of study drug and the effect of withdrawal of other active therapies.

The results at week 24, the end of the study, are summarized here. It was hypothesized that if omapatrilat reduced systolic blood pressure more than enalapril at week 8, it would also reduce the use of other antihypertensive agents from weeks 9 through 24, and this was observed. As summarized on the right-hand panel, subjects randomized to omapatrilat were significantly less likely to receive additional antihypertensive therapy than subjects randomized to enalapril. Despite receiving less top-dose study drug and less adjunctive therapy, subjects randomized to omapatrilat had consistently greater reductions in systolic blood pressure at week 24 as shown in the right-hand panel, about 3 millimeters of mercury more than subjects randomized to enalapril.

Now, these study findings were highly

consistent across patient subgroups. OCTAVE included about 7,000 patients over the age of 65, 2,000 over the age of 75, and 2,500 black patients. Omapatrilat reduced systolic blood pressure about 3 millimeters of mercury more than enalapril at study's end in each major demographic subgroup as shown on the right-hand column of this slide. Not surprisingly, reductions in blood pressure with both omapatrilat and enalapril were smaller in black patients than in others, but nevertheless blood pressure was reduced about 4 millimeters of mercury more with omapatrilat than with enalapril in these subjects.

OCTAVE also included a large number of patients with comorbid characteristics or other features associated with increased risk of cardiovascular disease. About 3,300 patients with diabetes and 2,300 patients with established cardiovascular disease were studied in OCTAVE. Omapatrilat produced consistently greater reductions in systolic blood pressure than enalapril, on the order of 3 to 5 millimeters of mercury, as shown on the right-hand side of this chart, in patients with severe hypertension, those with diabetes, atherosclerotic disease, isolated systolic hypertension, renal disease, or heart failure.

In summary, OCTAVE demonstrated greater blood pressure reduction with an omapatrilat-based regimen than with an enalapril-based regimen despite more use of top-

dose enalapril and more use of adjunctive antihypertensive therapy with enalapril.

The results of OCTAVE were highly consistent, regardless of patient demographics or comorbidity and regardless of the manner in which study drug was used.

Lastly, the greater blood pressure reduction observed with omapatrilat at week 8, the end of the study drug titration period, was preserved to the end of the trial despite the use of adjunctive therapy in order to reach a common blood pressure target in all patients.

The advisory committee has been asked to consider why the efficacy advantage observed at week 8 in OCTAVE was preserved at week 24 and whether this suggests that an omapatrilat-based regimen provides a reduction in blood pressure that cannot be achieved with a regimen based on enalapril or existing therapies.

OCTAVE provides a unique data set with which to answer this question. While we acknowledge that in many patients hypertension can be readily controlled with enalapril or other existing treatments, OCTAVE suggests -- and other clinical trials confirm -- that hypertension is difficult to control in many patients, even with multi-drug regimens. Therefore, for many patients the question is not whether omapatrilat can be used in place of a combination regimen, but whether omapatrilat should be used as part of

a combination regimen. The results of OCTAVE strongly confirm that a combination regimen which includes omapatrilat reduces blood pressure to a greater extent than a combination regimen containing enalapril because omapatrilat is a more efficacious antihypertensive agent.

The effect that greater drug efficacy can have on regimen efficacy can be most clearly appreciated in those most likely to require a multi-drug antihypertensive regimen, namely those whose blood pressure is difficult to control with single agents. In this presentation, the blood pressure changes at week 24 are summarized for study group 1 subjects stratified according to their baseline severity of hypertension; that is, from left to right, mild or JNC VI stage I, moderate or JNC VI stage II, severe or JNC VI stage III.

The difference between omapatrilat and enalapril at week 24 is present in all three groups, but it is most apparent in those with most severe hypertension at baseline in whom, as shown on the right-hand panel of the slide, the rate of use of adjunctive therapy was also the greatest. This suggests that the benefit of a more efficacious antihypertensive agent might be greatest in those most likely to require combination therapy, those with hypertension that is difficult to control.

Another representative group of patients with

difficult-to-control hypertension is those who remained significantly above blood pressure goal in spite of treatment with existing therapies. In data from patients randomized to OCTAVE study group 3 who continued to have JNC VI stage II hypertension in spite of treatment with two or more antihypertensives or three or more antihypertensives at baseline are shown on this slide. In these patients, the addition of omapatrilat provided significantly greater blood pressure reduction compared to the addition of enalapril, demonstrating the benefit of adding a more effect agent.

The FDA review has raised the question that the efficacy difference between omapatrilat and enalapril may be easily overcome with greater use of adjunctive therapy. I would like to make two important points here.

First, many of these difficult-to-control patients are already on multiple treatments and have limited options for additional therapy.

Second, many of these patients remain significantly above goal even after adding enalapril or omapatrilat, as illustrated here in these 700 patients in whom the rate of control with enalapril on top of three baseline meds is only 28 percent at the end of the study, and even with omapatrilat only 42 percent reached target. If there is opportunity to add more treatment, if there are

options, it would occur in both patients treated with omapatrilat and those treated with enalapril. And while the use of adjunctive therapy would increase with both drugs, the blood pressure reduction in the regimen with more effective components would still be grater.

Hence, in patients with difficult-to-control hypertension, a regimen containing omapatrilat would be expected to provide persistent benefit compared to a regimen using less effective agents due to the greater antihypertensive efficacy of omapatrilat.

To maximize the benefit this drug has to offer, we are focusing on patients with high cardiovascular risk and hypertension that is difficult to control with existing agents, and I'd like to provide you with some more data in patients not achieving blood pressure goal on current therapies.

I'll now present data collected in another group of patients with hypertension that's difficult to control with existing agents, namely those who are resistant to ACE inhibitor therapy. This group of patients is of particular interest since ACE inhibitors are widely used to treat hypertension and since omapatrilat acts in part through ACE inhibition. I'll review data from two sources, a study conducted specifically in ACE inhibitor resistant patients, study -73, and the large number of such

patients from OCTAVE.

This slide summarizes the design of study -73, conducted in patients who remained above blood pressure target despite aggressive ACE inhibitor therapy. Subjects with systolic blood pressure of at least 140 millimeters of mercury or diastolic pressure of at least 90 millimeters of mercury despite therapy with an ACE inhibitor at maximal or near maximal dose for at least a month were enrolled and, after a 2-week stabilization period, randomized to treatment with either omapatrilat starting at 20 milligrams and up-titrated to 80 milligrams, or lisinopril starting with 10 milligrams and up-titrated to 40 milligrams.

The lisinopril arm was intended to reproduce under blinded conditions the potential effects of continued therapy with maximal ACE inhibitor. All patients were treated with top doses of omapatrilat or lisinopril for 4 weeks prior to the final evaluation. Ambulatory blood pressure was used as the primary method for the assessment of treatment effect.

At study's end, 24-hour ambulatory systolic blood pressure was reduced 8.8 millimeters of mercury more with omapatrilat than with lisinopril. Blood pressure was also reduced more with omapatrilat than with lisinopril at each time point during 24-hour ambulatory blood pressure monitoring. While the differences between omapatrilat and

lisinopril were greatest during the daytime hours, a difference of 7 millimeters of mercury persisted at trough, 24 hours post dose administration.

The results of this study indicate that patients resistant to ACE inhibition are not equally resistant to treatment with omapatrilat and suggest that omapatrilat can be used as an alternative to ACE inhibitors to provide substantial additional blood pressure reduction in patients failing to reach target with an ACE inhibitor.

Of course, subjects treated with an ACE inhibitor alone could achieve additional blood pressure reduction through addition of a second or third agent. This study evaluated not only patients uncontrolled on ACE inhibitor monotherapy, but also those uncontrolled on ACE inhibitor as part of a combination antihypertensive regimen. In such subjects, the ACE inhibitor was discontinued at randomization while other antihypertensive medications were continued without alteration in dose.

As shown here, reductions in blood pressure were highly consistent whether subjects entered the study on ACE inhibitor monotherapy, as shown in the left-hand bars, or on an ACE inhibitor as part of a combination antihypertensive regimen, as shown in the right-hand bars. Numerically the reductions in systolic blood pressure relative to enalapril were greater in those who entered the

study on an ACE inhibitor-containing regimen than those who entered the study on an ACE inhibitor monotherapy, 11.5 versus 7.6 millimeters of mercury.

Now, OCTAVE also included over 4,000 subjects whose enrollment blood pressure remained above target despite therapy with an ACE inhibitor or ACE inhibitor-containing regimens. In these patients, prior treatments were discontinued at study entry and patients were randomized to either omapatrilat or enalapril.

Blood pressure was reduced consistently more with omapatrilat than with enalapril whether patients were receiving an ACE inhibitor alone at randomization or as part of a regimen containing one or more additional antihypertensives. Numerically the greatest reductions relative to enalapril of about 6 millimeters of mercury were observed in those receiving an ACE inhibitor plus two or more antihypertensive medications at randomization.

Now, the proposed target indication also includes patients with difficult-to-control hypertension who have comorbid conditions and other characteristics that put them at increased risk of cardiovascular events. As representative data for this population, the results from OCTAVE in subjects with diabetes and blood pressure above target at enrollment despite ACE inhibitor therapy are summarized here. About 1,000 patients are included in this

analysis.

Omapatrilat reduced blood pressure significantly more than enalapril in these subjects whether they had been treated with an ACE inhibitor alone at randomization as shown in the left-hand bars or with an ACE inhibitor-containing antihypertensive regimen in the middle and right-hand bars. Reductions in blood pressure with omapatrilat relative to enalapril ranged from about 5 up to 9 millimeters of mercury, and the greatest reduction was again observed in those receiving the most intensive antihypertensive regimen at baseline.

In summary, a large clinical development program has demonstrated that an omapatrilat-based regimen reduced blood pressure more than the regimens containing enalapril. This blood pressure advantage was consistent across patient subgroups regardless of the manner of the use of the study drug. And OCTAVE further suggested that the blood pressure advantage observed with omapatrilat in clinical trials can be maintained under clinical use conditions.

Lastly, data from OCTAVE, as well as data from other trials, indicate that in patients that cannot readily achieve blood pressure target with existing drugs, omapatrilat provides further blood pressure reduction that's not otherwise available.

Now, let's go on to safety. In a few minutes, I'm going to ask Dr. Kaplan to come to the podium to present an overview of angioedema.

DR. BORER: I'm sorry. Just before you do that, because these are a lot of data and there will be a lot of questions, maybe if it's okay we can stop here and ask questions to clarify the efficacy data, and then we'll move on to the safety and do the same thing.

Does anybody on the committee have substantive questions about the data? Tom.

DR. PICKERING: Yes. I have one general question. It's well known that ACE inhibitors' effectiveness is increased by sodium depletion or diuretic treatment, and I don't think in any part of your presentation you specifically referred to the use of concomitant diuretics. I don't think I've seen any head-to-head comparison between omapatrilat and an ACE inhibitor-diuretic combination, which many of us use in clinical practice. Do you have such data?

DR. LEVY: If I could refer to my backup deck for a moment. Thank you. Could I have slide HP-8?

What we've done here is summarize the blood pressure reductions at study end in patients who received a variety of additional therapies after week 8. On the left-hand panel are displayed the findings in those who received

hydrochlorothiazide in addition to either omapatrilat or enalapril, as well as those who received a variety of other antihypertensive agents. As you can see, both omapatrilat and enalapril have additional efficacy when supplemented by hydrochlorothiazide, but the blood pressure reduction with omapatrilat remains greater. And the same is true really regardless of the antihypertensive agent or class which is added on top of omapatrilat or enalapril.

DR. PICKERING: You are saying that no study has been done with a randomized direct comparison between omapatrilat and ACE inhibitor-diuretic combination. Is that correct?

DR. LEVY: Yes. We're not proposing that the drug be used in patients who can readily be controlled with an ACE inhibitor-diuretic combination. And the patients I've shown you are patients who are typically already treated with combination therapy in whom the option of adding a diuretic to an ACE inhibitor is no longer available.

DR. BORER: Are there other substantive issues? Bob.

DR. TEMPLE: This is to some extent the same question. But on slide 25 where you're looking at ACE inhibitor plus two or more antihypertensive meds, what would those antihypertensive meds have been? I ask because

it matters. For example, if they're all on beta blockers, you don't really expect too much more. The effectiveness overlaps. Were they all on diuretics, as they presumably should have been? What were they on?

DR. LEVY: The majority of these patients were on diuretics, and then, of course, the third med was a variety of medications, in some cases a calcium channel blocker, in some cases a beta blocker.

DR. TEMPLE: Okay, but again I ask because the question that I'm sure will come up repeatedly always is this extra 3 millimeters or 10 millimeters or whatever it is -- could you have done it just as easily by adding amlodipine? So, all of these things raise that question. I'm just trying to direct it there early because I think that's going to come up repeatedly.

So, those people would have mostly been -- it's not that many, but 169 of them -- on at least a diuretic, do you think? Do you know exactly?

DR. LEVY: Can we go back a slide? Again, this is a cut of a cut, but the previous slide, slide 24, is of a larger number of patients who were on an ACE inhibitor at randomization and failed to reach target. As you can see, there was almost 600 in the group on two or more antihypertensive meds. And yes, these patients are in general receiving an ACE inhibitor, in most cases plus a

thiazide diuretic and then a calcium channel blocker or a beta blocker.

DR. TEMPLE: You don't ave a precise breakdown of that.

DR. LEVY: We can provide you with that information later, if you'd like.

DR. TEMPLE: Okay.

DR. BORER: Paul.

DR. ARMSTRONG: My question is in the same area. Just to pursue this, if we're going to get more data to see later, not only would I be interested in the types of adjunctive therapies that were added in instances where one or other choice of therapy in OCTAVE was perceived to be inadequate, but the doses of those agents. In other words, were the doses of those agents pushed to equal intensity in the instance where it was perceived that the primary therapy had failed?

DR. LEVY: Certainly there's a wealth of data on that question. Let me provide you with the one patient subgroup where the data is most clearly defined. As mentioned, this was a simple trial. The case report form was simple, and the amount of information about study drug dosing is therefore limited. But for a few certain drugs, we do have specific dosing information, and perhaps I can show you some information there that will illustrate what

happens when omapatrilat is used rather than enalapril in patients who were receiving high-dose, aggressive antihypertensive regimens. I think they're representative of the whole study, but for this particular subgroup, we have very detailed information about dosing.

These would be our slides comparing the efficacy of omapatrilat and enalapril at week 24 in study group 3 subjects who entered the trial on a two-drug regimen, including amlodipine and hydrochlorothiazide.

DR. BORER: While you're pulling that up and looking for slides, Steve is our committee reviewer, and he'll have a number of questions I'm sure. But I had a specific question on the same issue and that was from your slide number 23 where the addition of lisinopril actually caused no change, an average .6 millimeter of mercury increase in blood pressure, when added on to other therapy. And I too wanted to know what the other drugs were, what their doses were, how you would explain that, what the population was. Were there some vagaries there that could explain the absolute lack of any activity of the ACE inhibitor in that population? So, while you're looking all this up, go back to your slide 23 also, if you would.

DR. LEVY: All right. Let me answer this question first and then I'll return to your question.

Again, in this group we have the most specific

information about study drug dosing and the doses of adjunctive therapy. Now, these are patients who entered the trial uncontrolled on two or more antihypertensive agents, which included amlodipine or hydrochlorothiazide, and for those two drugs we have the dosing information. These patients at baseline had blood pressures that remained at JNC VI stage II, systolic pressure of 160 to 169 or diastolic of 100 to 109. And their mean systolic pressures were about 166.

These patients were receiving a minimum of hydrochlorothiazide and amlodipine. The mean dose of amlodipine was 7 milligrams. The mean dose of hydrochlorothiazide was 20 milligrams. So, the patients were about split between amlodipine 5 and 10 and hydrochlorothiazide 12.5 and 25. About 40 percent of them were also receiving a beta blocker, and 10 percent were also receiving an angiotensin receptor blocker. So, over half of these patients were actually receiving three drugs at randomization.

They then received, in addition to their existing therapy, omapatrilat or enalapril. As I mentioned, these drugs were used very aggressively in the course of the trial. Over 60 percent of these patients were titrated to enalapril 40 milligrams, which is a dose that's considerably higher than that generally used in

clinical practice, and then some number of these patients received a fifth or a sixth antihypertensive agent in the course of the trial.

So, these represent really an extraordinarily aggressively treated group of patients in terms of the number of drugs and the dosing of those drugs. And there's still an advantage in both systolic and diastolic blood pressure reduction at the end of the study. So, I present these as representative. I happen to have the most detailed dosing information for these patients, but they're presented to you simply because you asked a question about dosing.

DR. BORER: Do you have any idea why 7 milligrams and 20 milligrams was the average? It's certainly not the maximum labeled dose of amlodipine, and the thiazide dose, though, one can go way up the scale. One might choose not to because of safety issues, but 20 milligrams is kind of low. So, why is it that those adjunctive therapies or those initial therapies were limited in those patients? Do we have any idea at all?

DR. LEVY: Well, you know, in practice physicians tend to prefer the use of low-dose therapies, particularly for drugs that do have dose-related toxicity. Amlodipine has a much higher incidence of peripheral edema at 10 milligrams than at 5 milligrams. That may have been

a factor in physicians' choice of 5 milligrams in some half of these patients, and thiazide diuretics also have a dose-related adverse effects that may have influenced the selection of study dose. But these are actually relatively high doses compared to those encountered in usual practice.

DR. BORER: Right, but that's not really the point. What's encountered in usual practice may be reasonable or it may be unreasonable, and I know that there are many reasons people may do things. That doesn't make them rational or right. The question is, do we actually have information about why people weren't given the higher doses? Maybe you don't, and I'm not suggesting you had to have such information but I'm just asking if you do.

DR. LEVY: No, we don't.

DR. BORER: Before you go on with Paul's issue, can you go back to your slide 23? Do you know anything about that group that received lisinopril on top of something else?

DR. LEVY: Again, this isn't OCTAVE. This is a trial that was specifically conducted in patients who were resistant to ACE inhibitor therapy. In this study patients who were on combination regimens discontinued the ACE inhibitor at randomization but continued all other medications. They were already on maximal or near maximal ACE inhibitor therapy at randomization. So, that meant

lisinopril 20 milligrams, enalapril 20 milligrams. What you see there reflects the replacement of their prior ACE inhibitor with study ACE inhibitor, which was titrated to 40 milligrams.

DR. BORER: Do you have any information about the characteristics of that population that would explain their relative resistance just for our edification?

DR. LEVY: Well, there were more black patients represented in this study and a slightly higher incidence of diabetics, characteristics which might be associated with diminished response to drugs which inhibit the renin-angiotensin system. But it was actually a quite representative hypertensive population.

DR. BORER: Paul, have you completed?

DR. ARMSTRONG: Yes.

DR. BORER: Steve.

DR. NISSEN: First of all, I really want to compliment BMS on one of the most extraordinary development programs for a hypertensive drug. The number of patients studied, the robustness of the data is really quite extraordinary. I think there a lot of insights, obviously, to gain from a 25,000-patient study.

I also wanted to say I really appreciated the review from Drs. Lawrence, Stockbridge, and Throckmorton. I think we had a really comprehensive package. So, we've

got a lot of information and I want to go through a little bit of it.

I wanted to begin by asking something about mode of action, and the question I want to get at is why does this agent have greater antihypertensive efficacy. I'll offer you a hypothesis, and I want to know whether there's any data to support it.

The hypothesis is that by increasing levels of natriuretic peptides, that there's a weak diuretic effect from the drug. So, what we're looking at here is something that looks like the combination of an ACE inhibitor with a very weak diuretic. As we all know, when you add a little bit of diuretic to an ACE inhibitor, you get a lot of bang for the buck. You get a lot of blood pressure reduction, even 6.25 milligrams of hydrochlorothiazide will add a few millimeters of blood pressure reduction to ACE.

Is that really what we're seeing here that we have in a single compound a drug that's combining a little bit of diuretic effect with an inhibition of the renin-angiotensin system? And any of your consultants, if you could shed some light on this, I would be appreciative.

DR. LEVY: If I can just make a few comments. That's an excellent question. Certainly when we began developing the drug, it was a major question. In our clinical pharmacology program, in which subjects were

actually studied in clinical research units and their intakes and outputs could be carefully measured, there was no evidence of a natriuretic or diuretic effect with omapatrilat at doses well above and below those studied.

In our hypertension development program, as I've shown you, patients who received a diuretic in addition to omapatrilat, experienced the same incremental reductions in blood pressure that one sees when adding a diuretic to an ACE inhibitor, suggesting that its additional antihypertensive effect is not mediated through diuresis. It appears to be the vasodilator effect of the natriuretic peptide that contributes to the antihypertensive effects of this drug. In particular, the drug may have a unique central vasodilatory effect on the large conduit vessels.

DR. NISSEN: You did formal salt balance studies and that sort of thing. Are those available for us? Because I think that would be very interesting to see is, in that first week after you start the drug, what happens to salt balance, not later on, but as I understand diuretics, what you see is an initial fall in sodium and then it returns to normal again. I'd be very interested in seeing any salt balance studies that you have.

The reason it's relevant I guess is let's suppose that that's right, that this is a drug that has

weak diuretic properties. Then it still might be true that adding additional, say, hydrochlorothiazide to the regimen would produce additional blood pressure reductions. I mean, if you go from 6.25 to 12.5 to 25 milligrams of hydrochlorothiazide, you see additional efficacy. It's highly relevant in my view because it speaks to Tom Pickering's question, which is, is the real comparator for omapatrilat ACE plus a little bit of diuretic? Is that really what we're talking about as a comparator?

DR. LEVY: Well, of course, we're not recommending that the drug be used in patients who can be controlled with ACE plus a little bit of diuretic. We're proposing it be used in patients who can't be controlled with an ACE-diuretic combination, and there's evidence that it provides substantial incremental benefit in those patients.

So, with regard to the mechanistic considerations, with a thiazide-diuretic, one would see a brisk diuresis within hours of administration of the drug, an excretion of 200 to 300 millimoles of salt. We don't see anything like that with early dose administration.

DR. NISSEN: So, there are salt balance studies that you can provide us to take a look at?

DR. LEVY: There are studies conducted in which urinary sodium excretion is measured over the first hours

of dosing and the first 24 hours of dosing, a time period in which the effect of either a thiazide or a loop diuretic would be unmistakable. And we don't see anything at all.

DR. NISSEN: Okay.

I wonder if you could bring up slide 11. There are some things I didn't understand here, and I really want to explore it.

Let's look at the add-on group, or group 3. Now, the entry criteria for group 3 was what entry criteria? What did you have to have to be in group 3?

DR. LEVY: These patients had to be uncontrolled on antihypertensive therapy with blood pressures at JNC VI stage II, or a systolic blood pressure of 160 to 179 or a diastolic blood pressure of 100 to 109. These patients at randomization continued their existing antihypertensive therapies and added omapatrilat or enalapril.

DR. NISSEN: I thought that's what I heard, and then I was confused because the baseline blood pressures in this group are actually lower than the minimum requirement to get in that arm of the trial. When I read this last night, I just couldn't understand how that could possibly happen.

DR. LEVY: Well, that's a very good question. Remember, patients could enter the trial by satisfying

either the systolic blood pressure criteria of 160 to 179 or the diastolic blood pressure criteria of 100 to 109.

Now, you made a very important observation. The systolic pressure is 166 which is within the target range, while the diastolic pressure is below. That reflects the difficulty in achieving systolic blood pressure control in populations. Failure to control systolic blood pressure is the primary reason for difficult-to-control hypertension. And Dr. Black is going to address this issue in more detail at the end of this talk. So, it's not a defect the study design. It really reflects the extraordinary difficulty that physicians have in bringing systolic blood pressure under control with existing medications.

DR. NISSEN: Well, let me tell you what I'm concerned about. Again, we're trying to tease out the group that might benefit here. So, this group 3 was going to be people who were just refractory. They couldn't be controlled on existing medications. When I see a group that's 166 over 97, it seems a lot less refractory to me than the entry criteria would look like. My guess is sometimes when you do a trial of 25,000 patients in less than a year, you've got to get patients in the trial, and so investigators tend to be a little more aggressive and maybe initial blood pressures were a little bit lower than

you wanted them to be. So, I'm not sure how refractory that group 3 is. It does color my interpretation of the data when I see that the average blood pressures are pretty low and really below the targets in that group. Do you follow me?

DR. LEVY: Perhaps I'll ask Dr. Black to comment at this point.

DR. BLACK: Yes, thanks very much, Elliott.

Steve, I just want to say that I don't think those are really low at all. That's the world through a diastolic window, not through a systolic window. The problem we have, as I'll show you a little bit later, is not that we can't control diastolic pressure. It's that we can't control systolic pressure. In fact, arteries get stiffer in diastolic falls if you leave people untreated. So, pulse pressure widens and I think that's the group you're looking at.

DR. NISSEN: Well, the reason this is germane is you've said several times that you want to target this drug at those people that are very, very difficult to control with conventional regimens. What I see is in OCTAVE, a 25,000-patient trial, in each of the three arms the blood pressures are not extraordinarily elevated. So, I know you have some people in OCTAVE that were very, very high, but I'm interested in understanding whether there is,

in fact, a target population identified here that would be optimally benefitted. It's harder when the average blood pressures in the trial are not as high as one might have expected.

DR. LEVY: Let me return to that point. Again, in these study group 3 patients, the systolic pressure at baseline is at least 27 millimeters of mercury above target on treatment. In those with diabetes, renal failure, heart failure where the treatment target is 130 millimeters of mercury, the blood pressure is 37 millimeters above target. If a patient walked into your office untreated with those pressures, you might be able to bring them down with one, two, or three medications. If a patient was already on two or three medications, the opportunity to reach target is very, very limited.

Again, we had patients in this group -- and I've shown you the results -- patients who were on two drugs at randomization, patients who were on three drugs at randomization. On three drugs at randomization with blood pressures in this range, the addition of very high-dose enalapril, making them on a four-drug regimen, plus other drugs, you still only get 28 percent of them to target.

DR. NISSEN: I agree that group is certainly a target group.

But I did want to look at the group that's

really much more severe. I know you did a study, 137-049. I'm sure you have those slides. I'd like to see that study because I think it helps us here.

DR. LEVY: Sure. Perhaps I could just begin by going back to the slide from our core deck showing the results in patients with severe hypertension in OCTAVE.

DR. NISSEN: Sure.

DR. LEVY: If I could have the table displaying the results by comorbidity. That's slide 16. Again, for patients who entered the trial off therapy, we could assess their underlying blood pressure. That's study group 1. And 1,000 of those patients had severe hypertension. If you were to include, as we did by design, those who entered the study on treatment on at least two antihypertensive medications, then the number with severe hypertension goes up to about 7,000. So, it's a very large experience. And the confidence intervals around the estimate of treatment effect are very narrow.

Now, in 1998 and 1999, we conducted an exploratory study in patients with severe hypertension. That study included about 160 patients, about two-thirds of whom were on omapatrilat and a third on enalapril. That study was designed to determine whether the drug effectively reduced blood pressure in patients with severe hypertension, and it did. It did not demonstrate a

statistically significant difference between the groups, and it was not intended or powered to do so.

DR. NISSEN: Do you have a slide with the data?

DR. LEVY: Sure. We can look for that and come to it a little bit later.

DR. NISSEN: I'd just like to see it because as I recall, the entry criteria for that -- there it is. That's the study.

DR. LEVY: This was a little bit different study population. The focus in registrational trials in hypertension has been on diastolic blood pressure, even though that's not the critical variable of the population. So, this study looked at patients with diastolic pressures of 115 to 130 off treatment. It's actually a very narrow segment of the severe hypertensive population.

DR. NISSEN: Okay, but nonetheless, these are pretty severe. So, it obviously does send us a signal that we'd like to see. Show us what happened with this group.

DR. LEVY: Can we see the primary efficacy results in this study? These are results at week 10. These are regimen comparisons. Virtually every patient was on multiple drugs by this time, many on three drugs, and blood pressure was reduced with both drugs. It's reduced about a millimeter of mercury more with omapatrilat than with enalapril in systolic blood pressure and about 2

millimeters of mercury more diastolic with omapatrilat than with enalapril.

DR. NISSEN: Did that result surprise you?

DR. LEVY: No. It's a small study and it was designed to compare regimen versus regimen. It wasn't designed to determine if omapatrilat reduced blood pressure more than enalapril. In fact, there was no planned statistical comparison in this study and it wasn't powered to make one.

DR. NISSEN: All right, fair enough.

DR. TEMPLE: Before you leave that, that's a pretty large antihypertensive study. It's not a small study.

DR. LEVY: I don't think that 60 patients in the enalapril arm is very large. In any case, it's a lot less than the 1,000 we have in OCTAVE.

DR. NISSEN: Actually there is a little discrepancy, Bob. In the FDA briefing package, the endpoints are shown, but they're actually opposite to that. They show actually that there was a little bit greater efficacy with enalapril than omapatrilat. I'm not sure which is right.

DR. THROCKMORTON: In this study?

DR. NISSEN: Yes, I think so. I'll pull it.

DR. THROCKMORTON: I don't think I included

this particular study review from the original efficacy. I'm looking at my original package, and I don't remember doing that because that study, as Elliott said, when we looked at it originally, was very small and had no statistical plan even associated with it. So, we did relatively less with it. But we can double check that.

DR. NISSEN: Fair enough.

I'm exploring with you because obviously one of the things that we're trying to weigh here is risk versus benefit.

DR. BORER: Excuse me just one second. There is a mention of numbers and they do appear to be in the opposite direction.

DR. NISSEN: I thought so.

DR. BORER: Severe hypertension in CV137-049. These pages don't have numbers on them, so I can't tell you where in the review it is. But it does say that the change from baseline seated diastolic blood pressure was similar for the two groups, minus 26 for omapatrilat and minus 29 for enalapril.

DR. NISSEN: So, they're reversed from what's in there. I understand the limits of the statistical comparison here. Your point is well taken.

Let me tell you what I'm trying to explore with you. We're trying to weigh here risk and benefit, and

obviously showing that in the very severe hypertensive, you can get them a much better chance to get them to goal has a real impact on our thinking about the relative risk and benefit of a drug. So, I was interested in 137-049, and I wanted to look at it with you because we just had one paragraph about it in our briefing book. And I wanted to understand what was done there, and I understand it wasn't a huge study. It doesn't compare to the 25,000 patients in OCTAVE, but I wanted to at least understand what it was all about.

Now, the next issue I wanted to go into -- and, Jeff, I won't take much longer because I think we want to move on -- is you compared to once-a-day enalapril. We had a rather extensive discussion yesterday on the issue of once-a-day versus twice-a-day drug dosage.

Now, the differences were about 3 over 2 millimeters, something like that, between once-a-day omapatrilat and once-a-day enalapril. One of the questions that I needed to have answered was, what might we have expected if the enalapril had been given as 20 milligrams b.i.d.? Remember now, we're going to try to calculate a benefit versus a risk. So, the differences between those two regimens is very, very important. What would the difference have been if we had given enalapril 20 b.i.d. rather than, say, 40 milligrams once a day? Any

information about that?

DR. LEVY: That's a very good question. I really can't speculate about that. We didn't do a study versus b.i.d. enalapril. We chose an enalapril dose regimen that reflects the way physicians give chronic therapy to patients in practice, which is once a day.

Now, we do have a variety of studies against other agents, studies in which the optimum effect of omapatrilat was compared to the optimum effect of those agents, and that includes comparisons with not only lisinopril and losartan, but also with amlodipine which is an extremely long-lived, once-a-day drug. There again there is superior efficacy.

DR. NISSEN: Well, let me tell you what triggered me to ask the question. Since you're going to present OVERTURE and I don't want to presage that, it's interesting that in OVERTURE you gave the enalapril b.i.d. and in the hypertensive patients, there was exactly the same blood pressure reduction between omapatrilat and enalapril given b.i.d., 12.6 and 12.7 millimeters. So, I was left saying, gee, what if OCTAVE had done that? Could that have completely erased the blood pressure differences between the two regimens?

DR. LEVY: Again, it's hard to imagine it would do that in patients whose blood pressure remains

uncontrolled. It's difficult to control with regimens like twice-a-day enalapril or twice-a-day enalapril plus a thiazide diuretic patients who need more therapy.

DR. NISSEN: Michael, you look like you have some thoughts about that.

DR. WEBER: I was going to suggest, Steve, that we take a look at the ABPM data because, in fact, that does show pretty good 24-hour efficacy for the ACE inhibitors as well. Do you have the ABPM data with the lisinopril study? Slightly different than enalapril.

DR. NISSEN: Wasn't lisinopril a bit longer-acting?

DR. WEBER: Yes. Do we have ABPM data for enalapril in the resistant --

DR. TEMPLE: Lisinopril I think is labeled for once-a-day only because it's got a very long half-life.

DR. NISSEN: So, I guess the lisinopril ambulatory blood pressure data I wouldn't consider relevant.

You know, it's really an important question, and I know I'm kind of being a stickler here. But if I'm going to calculate the potential benefit versus the potential risk, I've got to know how much the difference between enalapril and omapatrilat is. If enalapril is given in an optimal way, that might be b.i.d.

DR. PACKER: Steve, I think you're asking a very important point. I was in the audience yesterday and I know the committee was discussing what constitutes a fair comparison. Would it be appropriate to compare a once-a-day drug which is being proposed for once-a-day use against a drug which is most commonly used and includes a labeling for once-a-day use.

Having said that, there is an extensive experience with the comparison of once-a-day omapatrilat to twice-a-day enalapril in OVERTURE. I'll be reviewing OVERTURE, but I just wanted to address the question about blood pressure.

OVERTURE was a heart failure trial, not a hypertension trial. I think it would be fair to say that hypertension specialists tend to pay more attention to how they measure blood pressure than heart failure specialists who tend to think of blood pressure as being a general phenomenon and generally estimated. That creates a lot of noise in clinical trials.

Second is that the blood pressure measurements were made at trough in OVERTURE before the next dose of the drug, and there are considerable data from another heart failure trial called the IMPRESS study comparing omapatrilat once a day with lisinopril once a day, which is also approved once a day for heart failure, showing that,

yes, the blood pressures with omapatrilat and lisinopril come together at trough, but there's a huge difference during the day. Therefore, if you look at the cumulative effect over 24 hours, there's still a major difference between omapatrilat and the comparator ACE inhibitor. We couldn't document that in OVERTURE because we only have trough blood pressures.

DR. NISSEN: Would it be safe to say, Michael, whoever -- let me ask you this. Would it be safe to say that a regimen of 20 milligrams b.i.d. of enalapril might reduce blood pressure over the 24-hour period more effectively than 40 milligrams once a day? Would it likely narrow that gap of 3 over 2 millimeters or would it not?

DR. WEBER: It probably could, but I can't be certain of that, Steve, because certainly there have been plenty of other trials with enalapril given once a day where, in fact, I thought it did rather well throughout the 24-hour period. In fact, our experience with ABPM would suggest that enalapril may be fractionally better twice a day, just as you could say the same with losartan. In fact, we know that would be true. But still, we're talking about a very, very minimal advantage.

DR. NISSEN: 1 or 2 millimeters?

DR. WEBER: 0 to 1, .5 to 1.

DR. NISSEN: I guess the answer is we really

don't know. Is that a fair answer?

DR. WEBER: Yes.

The other thing too is omapatrilat is a long-acting drug. It gives you 24-hour efficacy, but you might have noticed from the ABPM data that towards the end of the dosing interval its advantage compared with the ACE inhibitor is getting less. You could argue that omapatrilat twice a day would be significantly better than omapatrilat once a day as well. So, I'm not sure how far we would want to take this particular argument.

DR. NISSEN: Well, I guess I wouldn't buy that necessarily, Michael, and the reason I wouldn't is that I'm a clinician and I've got a choice. I can give an agent with a more adverse safety profile once a day and take a risk of angioedema, or I can give a drug that's got a better safety profile twice a day. That's a very relevant consideration regarding approvability because if I could get the same blood pressure reduction by giving a safer agent twice a day, it would be hard to argue in favor of the less safe agent once a day I think.

DR. WEBER: Yes, but let me remind you of the patients who are resistant to ACE inhibitor, the study that Elliott showed before. The difference was really quite considerable between omapatrilat and enalapril in that setting, and I don't think giving enalapril twice a day

there would have really compensated for those kinds of millimeters of mercury.

DR. NISSEN: I have two other brief questions, Jeffrey, if you don't mind. A couple of interesting things.

I was very struck by your slide number 6, if you want to show that. There's an interesting question that it raises. So, in 037 you were studying African Americans, and in 030 the comparison was amlodipine. So, given the fact that lisinopril didn't work as well in African Americans -- and neither did omapatrilat -- I'd be interested in whether you have any comparative data comparing omapatrilat to amlodipine in African Americans. Did you do any of those comparisons?

DR. LEVY: Well, there were small subset comparisons within each of these trials that are done, and about 10 percent of the subjects in each of the trials in unselected populations tend to be African Americans. In general, all those subgroup cuts are very consistent with the overall study results. There's a superior efficacy for omapatrilat.

DR. NISSEN: I seem to remember somewhere in Dr. Throckmorton's review some studies where that comparison was made where, in fact, in that subgroup omapatrilat actually produced less effect than amlodipine

in the African Americans. I'm not surprised by that, but it's an interesting issue about choice of drugs in patients. There the risk-benefit really does shift quite a bit.

Doug, didn't you review that somewhere? Do you have that, Jeff?

DR. BORER: I think the statement is correct that in general the results look qualitatively similar by race. There may be a little bit more effect in non-black than black, but the results are qualitatively similar.

DR. LEVY: If I could comment, though, it's not our intention that omapatrilat should be used in patients who can readily be controlled with a safer agent. Particularly in black patients, we surely are not suggesting this drug should be used in place of a dihydropyridine calcium channel blocker in a patient who could be controlled on those drugs.

DR. NISSEN: I have one more brief question. The other questions I have on efficacy really relate to the issue of target organ protection, but I think I'm going to wait on those, Jeff, until after we hear from Henry and so on.

So, the one final question I had was on your slide number 3. I want to make sure I understand the entry criteria. So, this is the group you're proposing the drug

is most likely to benefit. Was this criteria of presence of cardiovascular disease an entry criteria for OCTAVE?

DR. LEVY: It was not an exclusion criteria.

DR. NISSEN: But it wasn't necessarily an explicit one.

DR. LEVY: Well, I've shown you about 2,300 subjects had a history of MI or stroke or overt atherosclerotic disease at baseline. Heart failure was a small number, but there's of course a much larger number in the OVERTURE study.

DR. NISSEN: I want to come back to this later, but I do want to know subsequently. Since this is the population you're suggesting we should target with this drug, I will want to know more about studies done in such subgroups because, obviously, if you want to use a group in a subgroup, you've got to know a lot about it. So, I'll be interested later to hear about those people with known target organ damage, those people with post-MI, those people with three or more cardiovascular risk factors because, again, looking at risk-benefit, we need information about those groups if those are going to be the target groups that we're going to want to treat.

DR. LEVY: Right.

DR. BORER: Two final questions that I have for you. Again, you may not have specific information about

this, and if so, you don't. But why were patients who were not adequately controlled stopped at two drugs? You had a number of patients who were given one additional drug, two additional drugs, or three additional drugs. And if they were not adequately controlled with two drugs, still a fair number continued on two drugs. Why was that or am I misunderstanding?

DR. LEVY: I'm not sure I understand the question. If you could point to a specific slide.

DR. BORER: Why if somebody's blood pressure isn't controlled would you not add additional drugs to try to control them? Was there something in the protocol that would have precluded that? Was there some suggestion in the selection algorithm that would have influenced that? I mean, if somebody's blood pressure isn't controlled, in general you'd want to continue to push the dose or push the number of drugs until you get it controlled. But I inferred from your slide -- and I'm sorry I didn't write down the slide number -- that a number of patients were given one additional drug or two additional drugs and still weren't controlled but continued on that regimen rather than being given an additional drug.

DR. LEVY: You don't know the slide?

DR. BORER: No.

DR. LEVY: I think there may be a

misunderstanding, but I'll try to clarify that.

DR. BORER: I can probably find it easily enough here.

DR. LEVY: What I'd like to see is the slide from the core deck -- not this slide. Bear with me for a moment.

DR. PICKERING: I think it may be the protocol design. There were only two visits after week 8 -- is that right -- at which they could add additional drugs.

DR. LEVY: Let me first go to slide 20 in the core deck. I don't know if there's a misconception here. The number of meds. Those are the medications which the patient was receiving at study entry. Now, of course, there was no restriction on the number of medications that a patient could receive during the study.

And your point is a good one, though. If patients remain uncontrolled, physicians will continue to add drugs, and that's a very important point. They would do that. Obviously, most of these patients are not reaching target at the end of the study regardless of therapy. So, physicians would add drugs to both omapatrilat and enalapril.

DR. BORER: But did they? What I'm asking you is were there patients whose blood pressure didn't meet the target who were not on three drugs or more?

DR. LEVY: Yes.

DR. BORER: And why was that?

DR. LEVY: This is a 24-week trial. There are a discrete number of opportunities to add adjunctive therapy. Not every patient was brought to a three-drug regimen. Not every patient could be.

DR. PICKERING: Again, I think it was only weeks 8 and 16 that they had the opportunity to do that, so there was a limit to how many additional drugs you'd be able to add or dose-titrations you'd be able to do.

DR. LEVY: I think the larger question, though, is what can be accomplished with addition of a fourth, a fifth, or a sixth drug in patients who are multi-drug resistant. Maybe Dr. Black can speak to this question.

DR. BLACK: If I may, Jeff. This a practice-based study. You can, when you're doing a protocol, just encourage. You can't force necessarily a lot of physicians -- and there were lots of physicians in this -- to continue to add drugs. I'll show you some data late from our CONVINCE trial about what people used and where we ended up, another practice-based study with a fairly strict protocol, but we could not, in fact, insist that people went on. I think it's much like the question of why 7 milligrams of amlodipine and 20 of hydrochlorothiazide. I think people in practice dealing with individuals won't

necessarily go to the top dose.

DR. BORER: No, I understand, and that's a very reasonable response.

My point only is that the fact that people don't -- and this is not a value judgment here, but you're proposing a very extensive and intensive education effort -- it's laudable; it's wonderful -- to try to make sure that pharmacists, patients, and doctors all know about the risks and minimize their impact, and I think that's wonderful. I'm just wondering if that same kind of intensive effort were used with regard to managing high blood pressure in the first place, we wouldn't have so many people on 7 milligrams or 20 milligrams of adjunctive drug and might have better blood pressure control.

And that's not your responsibility or anything like that, but I don't think we should judge the results here based on the fact that, well, this is a practice-based study and doctors don't always do what would be done in an academic medical center. That may not be the appropriate conclusion from all this.

But I'm sorry. Go ahead.

DR. BLACK: Yes. I think you reflect the frustration we had when we wrote the Joint National Committee report in 1997, looked at data on how poor control was in spite of a 25-year history of a very

effective program. We did increase things. We've stopped and we need a much more aggressive physician and patient and pharmacist education program to improve control in general. We're not at all happy with 27 percent. NHANES IV looks as if we've improved things extremely little in spite of our awareness from JNC VI that this wasn't getting anywhere. We made some adjustments in JNC VI to try to make that more obvious, concentrate less on what drugs people use, but getting to a goal.

DR. BORER: Steve.

DR. NISSEN: Jeff, just to answer, I did find the comparisons that I was looking for with African Americans. If you want to see it, it's FDA table 7.12G.3. And I can't give you a page number, because there aren't any page numbers on there. But John Lawrence did the analysis.

What it shows is is that in the study 137-030, which was the amlodipine comparison, in black females omapatrilat was 7.9 millimeters worse than amlodipine with a p value of .01, and in black males it was 1 millimeter worse with no significant p value. So, there does appear, in fact, to be a racial difference, at least in the amlodipine comparisons, with omapatrilat being nominally worse in African Americans, but better in white males and females. So, it's a consideration here that I think

probably needs to be out and discussed because obviously it's exactly that population where the risks of angioedema are the greatest.

DR. BORER: Okay, if there are no more questions, thank you that was very informative.

DR. FLEMING: On slide A-5, you're defining this configured target population. Can you show us -- because this, in essence, now is going to create a focal data set, I assume, from your perspective -- the population that meets these criteria in OCTAVE, baseline characteristics for the two arms and what the actual results were in terms of blood pressure control, as well as what the differences are in overall clinical endpoints in this group of patients in OCTAVE?

DR. LEVY: We've not prepared a pooled analysis in which all these patients are put together. I've shown you data regarding efficacy in patients with severe hypertension and data in patients with diabetes whose blood pressure is difficult to control with existing agents. We have data on efficacy in some of these other populations, which I'd be happy to show you as well.

DR. FLEMING: This is your target group that you're going to request be viewed as a group in which we will, hopefully, have a favorable benefit-to-risk. Correct? So that basically is it correct to say you would

like to label the drug with this as the target indication?

DR. LEVY: The label is something that will be developed through discussions with the FDA. This is the intended target population.

DR. FLEMING: So, after the break, could you provide us, for this subpopulation of the trial, what the primary analysis would show for blood pressure control, differences in clinical events, and comparability at baseline?

DR. LEVY: Just to be clear, we've not done a pooled analysis in which we select all patients.

DR. FLEMING: I'm asking could you do so.

DR. LEVY: I don't know if we can do that between now and the break.

DR. FLEMING: Not between now and the break. Could you sometime after the break prepare that?

DR. LEVY: We'll certainly do our best.

DR. FLEMING: Have you not done this at all?

DR. LEVY: We have not prepared a pooled analysis of all these patients. I'll consult with the team. We'll do the best we can.

DR. BORER: What about each group individually? You've got four groups. Do you have data on each of the four groups?

DR. LEVY: Yes. I've shown you patients with

severe hypertension who are represented here. I've shown you data for those with diabetes. There's data for other patient populations as well. I'd be happy to walk through all of that in detail. We have an enormous database. But as I say, we haven't put them all together.

DR. BORER: Would you accept that, Tom, looking at each subgroup individually?

DR. FLEMING: It's perplexing to me that we've done a major trial here. We're recognizing that risk was in excess of what we had anticipated. We make the logical conclusion that it might be that there is an important subgroup for which benefit could be particularly substantial. So, we define that subgroup, and we propose that this group be what we focus on as a retrospectively defined subgroup. And yet, we're not able to show what the overall benefit is and what the risk is in that subgroup. I'm assuming we can define whether or not the 25,000 patients individually would fit into this subgroup, so we ought to have been able to, in a fairly straightforward fashion, define what would be the primary efficacy outcomes and the safety outcomes in the subgroup.

DR. BORER: Doug?

DR. THROCKMORTON: Jeff, a minor thing. I looked back at the study 049, which was the relatively smaller study on resistant populations, and in fact, those

two numbers that are in your briefing document are reversed. Again, I wouldn't make terribly large amounts out of them, but for what it was worth, the directionality was not different. That is, omapatrilat had the directionality towards a greater reduction than enalapril in that trial, which is the opposite of what's in the briefing document.

DR. BORER: Why don't we go ahead with the safety data and we'll come back to some of these efficacy issues later in the presentation.

DR. LEVY: In a moment, I'm going to ask Dr. Kaplan to come up to provide you with an overview of angioedema, but before I do, I'd just like to briefly provide a summary of the safety database.

The safety of the drug was characterized, as you know, in an extensive clinical development program, including about 35,000 hypertensive patients, 19,000 of whom were treated with omapatrilat. This, as you know, represents about 5 to 10 times the experience typically described in a hypertension new drug application. Large numbers of subjects were exposed to each of the proposed target doses. 13,000 were exposed for more than 3 months and about 1,500 for more than a year.

This extensive experience has provided an unusually clear profile of the safety of the drug. The

overall incidence adverse events, serious adverse events, and discontinuation due to adverse events has been shown to be comparable for omapatrilat and enalapril. The risk of angioedema has also been clearly characterized and shown to be three times higher than with enalapril.

Because of the importance of angioedema in the assessment of omapatrilat, I'm going to ask Dr. Kaplan to come to the podium now. Dr. Kaplan is an angioedema expert who will provide a brief presentation on the pathogenesis and clinical spectrum of this entity before I return to complete the safety presentation. Dr. Kaplan.

DR. KAPLAN: Thank you very much, Dr. Borer, members of the advisory panel, and guests. It's a pleasure to be here today. What I'm going to try to do is give you a little overview about what angioedema is and what are some of the agents and circumstances in which it occurs.

I'm Professor of Medicine at the Medical University of South Carolina. I'm a clinical allergist, so I see angioedema all the time. And my research for 30 years involves the mechanisms of formation and destruction of bradykinin, which is directly germane to the drug that we are discussing today.

Now, angioedema is due to dilatation of small venules in the deep dermis of the skin. It's caused by a variety of vasoactive substances, but the vessels dilate,

leak fluid, and cause swelling. And that's the common denominator of angioedema.

It has a predilection for various sites in the body, the most common of which are typically the face, particularly where tissues have low turgor. The most common site is the lip, but it often involves the eyelids, with periorbital edema, the cheek with an asymmetric swelling of the face. It can affect the tongue and it can affect the pharynx. When people have pharyngeal swelling, they will feel as if they are choking, even though their airway is not compromised. They will have difficulty swallowing and difficulty eating. On occasion angioedema will affect lower down and hit the larynx, and particularly we're concerned about vocal chord edema because then you're at risk of asphyxiating. It's uncommon but, nevertheless, there's a finite percentage who will have it. Other sites of angioedema are hands, feet, and genitals.

Among the common etiologies that we see of angioedema solo, without hives and without other manifestations, are a hereditary disease known as hereditary angioedema because the patients are deficient in a blood protein known as C1 inhibitor. In the absence of that C1 inhibitor, they overproduce bradykinin and that has now been proven to be the cause of the swelling and the hereditary disorder.

Similarly, the most common cause of angioedema that is exogenous -- that is, drug induced -- currently are ACE inhibitors. When you inhibit the angiotensin-converting enzyme, you not only prevent the conversion of angiotensin I to angiotensin II, but you're inhibiting one of three enzymes that are involved in the degradation of bradykinin. Therefore, by inhibiting degradation, bradykinin levels will tend to rise.

I should add that of those three enzymes are ACE, a plasma carboxypeptidase that is called carboxypeptidase N, and neutral endopeptidase. This drug inhibits two out the three, and that does distinguish it from ACE inhibitors because, given that information, the likelihood of bradykinin levels rising even more than you would see with an ACE inhibitor is at least theoretically possible and could account both for efficacy, as well as side effect.

Anaphylaxis and angioedema are different, and the reason I'll make a few particular comments about that is because they're often confused, and when patients present to the emergency room with angioedema, they often are treated for the other entity.

Angioedema, when it is due, let's say, to bradykinin in particular -- and that is in the hereditary deficiency, in the drug-induced -- typically evolves over

several hours. An average might be 2 to 4 hours. But particularly severe cases may be more rapid and progress within an hour or two. We are not, however, talking a few minutes as is the case with anaphylaxis.

If you have facial swelling, in particular, I want to point out that patients typically are keenly aware of this even if they've never experienced it before in their life. A little lip swelling, a little eye swelling, just a little tongue swelling has people complaining early on. It's important because if we're going to talk about education, then it's important to have patient awareness early on to know that something is going wrong and be prepared for that eventuality.

How do you treat angioedema if it is due to bradykinin? Well, there are very few things that work and none of them are specific. People are often given antihistamines. That's, of course, worthless. They're given steroids, almost equally worthless, and it takes five hours for them to work. Epinephrine will work because it's nonspecific. It will constrict the vessels that are leaking and it will retard the angioedema from continuing. It will not take it away. It is just gradually then reabsorbed. So, the goal is to stop progression.

It is important also to note that the one that we're really worried about is laryngeal edema because it's

the only one that causes airway compromise. I don't think I've ever seen a case of laryngeal edema that occurred solo without some other angioedema manifestation occurring with it. Usually lip swelling starts it. You may get tongue swelling, some pharyngeal swelling, and then the person complains of respiratory distress, first usually hoarseness, and then if it progresses, stridor.

In this last slide, I'm contrasting anaphylaxis with a drug-induced or hereditary angioedema, meaning the bradykinin-induced process. Anaphylaxis can occur in minutes. Infuse somebody with penicillin who's allergic to it, be stung by a bee while you're gardening and you're allergic to bee venom, and within a minute or two symptoms can begin, are often with generalized pruritus, followed by urticaria, angioedema, and then other manifestations. The patient will also often complain of like something really bad is about to happen, and we call it an impending sense of doom, if you will. But angioedema of the sort we're talking about doesn't evolve in quite that way.

In addition to the cutaneous manifestations, the key to anaphylaxis is that you now have cardiovascular manifestations and the hypotension and shock. That does not occur in the hereditary angioedema, nor does it occur in the drug-induced swelling.

Anaphylaxis can cause two syndromes, if you

will, with regard to respiratory embarrassment: classical asthma where the person starts to wheeze and really has difficulty expiring; and laryngeal edema. Laryngeal edema is theoretically common to both. Bradykinin can do that solo. You don't get asthma in patients with this, but as you know, you get cough with ACE inhibitors.

To our knowledge, bradykinin is the only mediator of the angioedema that we are talking about whereas in anaphylaxis you release histamine, leukotrienes, platelet-activating factor, an array of cytokines, and just multiple vasoactive factors.

The treatment for anaphylaxis is, of course, epinephrine. Anaphylaxis tends to rebound. You can have somebody that has anaplylacted, but they're in the emergency room and they're making it. You've given them treatment, they start to feel better. You can be seduced to think that they're okay and stop treatment, and then five hours later, the syndrome may come back, not quite as bad, but it's there. Steroids stop that which is why it should be given, but it's not the first thing that you do. They also need to receive IV fluids and, of course, IV antihistamine such as Benadryl which does counteract the histamine.

In the drug-induced, if they receive all of these things, the only one that does anything is the

epinephrine. Therefore, as you'll probably see, many patients that recover, even in an emergency room setting because they have gone there, who do not receive epinephrine but received all those other drugs, have spontaneously resolved without any treatment.

Thank you.

DR. BORER: Does anyone have any questions? Yes.

DR. NISSEN: Given what you said, there's an obvious strategy here for risk limitation that I had wanted to explore with you. If you had a drug that you knew had the potential to produce this, would it be prudent to give these patients an Epi-Pen? I know many of my patients who have had reactions to bee stings and so on carry that around. Could the sponsor here mitigate against this by giving every patient who is given omapatrilat an Epi-Pen so that they could self-inject with epinephrine if they get stridor?

DR. KAPLAN: Number one, of course, it would be a possibility which would theoretically be helpful and, if you had a reaction, would certainly tend to stop it.

There you have to balance. Now, the patient population that you're dealing with, if we're going to talk about the use of this drug in the most severe hypertensive who may have heart disease, arrhythmias, and who knows what

else, now having them self-administer epinephrine has some risk associated with it. You might not want to willy-nilly give it to everybody, and if you're going to do it at all, it's either all or none. Therefore, you'd have to somehow rationalize how many people would have the side effect of the epinephrine that was worse than what was happening to them. Perhaps it would be -- I'm just giving you the counter-argument -- better to select out those who have the most severe swelling, get them to the emergency room promptly and let some physician make a decision as to whether it's appropriate to give epinephrine or not. But I think it is a point well taken, and it is at least one of the things that could be considered.

DR. NISSEN: Suppose a patient is -- let's say, African Americans who had, I think, about a 1 in 18 or 1 in 19 chance of developing angioedema in OCTAVE. Would that be a high enough risk group that you might think about it?

DR. KAPLAN: Yes.

DR. NISSEN: And smokers again, it was about 1 out of every 27 smokers got angioedema. That might also be a good target population.

DR. KAPLAN: Yes. And I wouldn't argue the point with you. My only concern would be that I'm sure among the smokers and the black hypertensives are people with some of the most complicated other things that are

cardiac that you would have to deal with.

DR. BORER: Let's go Tom and then Susanna and then Paul. Tom.

DR. PICKERING: Thank you. I wondered if anything is known about C1 inhibitor deficiency in African Americans as compared with whites.

DR. KAPLAN: A C1 inhibitor deficiency is slightly less statistically of African Americans than in caucasians. Of course, it's rare to start with. That's in the hereditary disorder. There's a second form that is acquired and there the incidence is equal. It relates mainly to lymphoma. There are some people with lymphoma who express tumor antigens to which you make antibody. So, you have an immune complex and you fix-complement, and you can do so in massive fashion. You can fix so much of the first component of complement that the C1 inhibitor, which is the inactivator now binds to the activated first component and gets consumed. If the level of C1 inhibitor drops below 25 percent of normal, you're now at risk for having angioedema. So, the acquired form in lymphoma is a second type -- a third, if you will -- of bradykinin-induced angioedema, and there the incidence would be proportional to the incidence of the lymphoma in the population.

DR. CUNNINGHAM: I was wondering what you know

about why smokers and African Americans are at greater risk for angioedema.

DR. KAPLAN: Knowing what I do about bradykinin, I certainly have thought about it and I could not answer the question. I don't know. Particularly the smokers. There are some data comparing blacks and whites with regard to end organ responsiveness to bradykinin with some interesting data that might explain that, at least in part, but there's nothing on smoking.

DR. BORER: Paul and then Doug.

DR. ARMSTRONG: Dr. Kaplan, first of all, thank you for contributing to my continuing medical education.

I'm interested in your thoughts about the epidemiology of angioedema in the general population, especially in the aging general population. I'm interested in your comments about the frequency of new onset allergy in the aging population such as, for example, fish or medicines or pollens, and the implications of those phenomenon in a patient taking a medicine that would inhibit bradykinin.

DR. KAPLAN: The incidence of a food allergy goes down in an aging population and therefore allergic urticaria and angioedema due to a food allergy is actually lower.

The most common disorder that we see that is

not related to a specific allergen -- somebody walks into your office and says I've had hives and swelling for five months. I have no idea what's going on. I saw my internist, and they find nothing wrong with me. That turns out to be an autoimmune disorder due to, in part, at least in half the people, of a circulating antibody to the IgE receptor. So, the antibody cross links the IgE receptor just as if you had an allergen and they have waves of urticaria and angioedema that can last months to years. That is common throughout the population in all age groups, but I think in terms of allergy per se, even though it's going up in incidence in our population, it's almost all hayfever and asthma. It's not allergic urticaria or angioedema, and foods, in particular, goes down as we age.

DR. ARMSTRONG: So, a patient who develops late allergy for whatever reason who's taking an agent that inhibits bradykinin is no more likely to develop angioedema?

DR. KAPLAN: That's a tough question, but it has to be focused now only on an allergen for which angioedema is one of the manifestations. In other words, if you have hay fever and asthma, it's no more or less likely to be affected by an ACE inhibitor, nor will the allergen cause angioedema per se just because you're on the drug. On the other hand, if you give me a circumstance in

which angioedema might otherwise occur anyway and you are on an ACE inhibitor, you'd be more likely to get it, even though the pathogenesis then would be multifactorial.

DR. ARMSTRONG: Do you think that the exclusion criteria in OCTAVE -- and there was some exclusion criteria associated with a history -- I was looking for exactly the criteria. I can't find them at hand, but what I'm trying to get at is how effective the exclusion criteria in OCTAVE precluded a higher incidence of angioedema in a hypertensive treated population then would otherwise have been the case, if you follow my drift.

DR. KAPLAN: I know there's no way of predicting, which is ideally what you'd like to do, as to who will have angioedema to any of these drugs. I'm sure there's an explanation. It could be some subtle, genetic polymorphism in ACE or other things that are involved with bradykinin, but we just don't know. So, I'm not sure whether I can be more specific in answering your question. Others involved with the study might be able to chime in because I'm not that close to it.

DR. ARMSTRONG: There's a statement about any drug-induced rash of any kind would have been an exclusion criteria in OCTAVE, for example.

DR. LEVY: I'd like to clarify that because that's not correct. Patients with a history of multiple

drug sensitivities with a history of drug rash to two or more drug classes were excluded with the study, not patients with a history of a rash to any medication.

DR. ARMSTRONG: Do we know how many patients were excluded for that reason, Dr. Levy?

DR. LEVY: There's no way to know.

DR. KAPLAN: I could comment on that. There is a syndrome not well understood, a multiple drug hypersensitivity syndrome. A patient comes in and gives you a list of 10 medications. They get rashes to all of them. They go from one antibiotic to another, phenobarbital, an antihypertensive, and it cuts across classes of compounds and so on. It's reasonable in a study to eliminate them because they always come in and react to something, and you're just going to get into trouble.

DR. BORER: Doug.

DR. THROCKMORTON: Just one quick question. The statistical reviewer from the FDA appropriately pointed out that the number of cases of angioedema in this data set offers an unparalleled opportunity to look at angioedema and did some modeling as far as risks and things like that. I wonder if you could comment -- and you may be talking about this later, in which case it can come up later. Is there anything about the angioedema that you saw in this data set that suggests that it's of a sort that's different

than the kinds of angioedema that you've been talking about up to now?

DR. KAPLAN: It's a very important question, and the details you'll hear in a few minutes by Dr. Levy. The differences are quantitative but not qualitative. A severe patient on enalapril looks like a severe patient on omapatrilat. A mild patient looks like a -- I could not qualitatively -- and as a member of the review group, we tried to determine who has angioedema, is it drug-related, blah, blah, blah. I see angioedema due to ACE inhibitors all the time. That I could not distinguish. So, it's not qualitatively different, but it may be quantitatively different.

DR. BORER: Can I just follow that up? Because I was struck by the model also in reviewing this and I was going to ask the question later, but I think you're the right guy to ask.

When I looked at that model, my inference was if only we knew how, we could identify the people at risk. It was a three-group fit that best fit the curve. I'm inferring from what you said earlier, that we have no basis --

DR. KAPLAN: No marker.

DR. BORER: -- to identify risk. I don't know if any work is going on within the company to try to do

that. I assume there is, but right now there is no basis. Is that correct?

DR. LEVY: Let me just mention that we've had some ongoing work in that area, and perhaps once you've seen the safety data, we can share some of that work with you.

DR. BORER: Tom.

DR. PICKERING: As a follow-up to Dr. Throckmorton's question, is there any suggestion that the rate of progression of symptoms might be different in the omapatrilat than enalapril patients?

DR. KAPLAN: I don't think so. I think that when you see the data, the number that were considered "severe" was greater, but in terms of rate of progression, they looked exactly like what I'm used to seeing with any ACE inhibitor.

DR. BORER: Why don't we go ahead then. Thank you very much, Dr. Kaplan.

DR. LEVY: I'd like to thank Dr. Kaplan for that very interesting presentation and go on and describe for you in more detail the safety and particularly the problem of angioedema with omapatrilat.

Because the procedures used to assess angioedema in studies prior to OCTAVE and in OCTAVE were different, I'll describe the findings separately.

In studies prior to OCTAVE, angioedema was reported using standard procedures for reporting adverse events. The investigator typically provided a brief text description of the event which was then assigned a diagnostic code for the purpose of tabulation. The diagnostic codes were assigned using a dictionary based on the International Classification of Disease, or ICD-9. These procedures for reporting and classifying angioedema, which were identical to those used for the classification of all other adverse events, introduced certain limitations.

The ICD-9 based coding system assigned potential angioedema events to several different coding terms, depending on the actual verbatim text provided by the investigator. The most commonly used terms are "angioedema" and "head and neck edema." And while the term "angioedema" appeared to be quite specific for the event angioedema, the term "head and neck edema" was not specific, and the adverse event reports themselves didn't provide sufficient additional detail to further assess these potential cases.

The findings of studies conducted prior to OCTAVE are summarized here. A total of 44 cases of angioedema were reported. An additional 40 cases of head and neck edema were reported, which may have been

angioedema. These are shown on the right. 4 subjects experienced angioedema with airway compromise which required mechanical airway protection, and it was these findings reported in the prior new drug application which prompted the FDA to ask if the incidence and severity of angioedema were greater with omapatrilat than that historically reported with ACE inhibitors.

In reviewing these data, we observed that the rate of angioedema appeared to be lower in subjects who began treatment with a dose of omapatrilat of less than 20 milligrams compared to those who began treatment with a dose of 20 milligrams or greater, in this case .45 versus 1.35 percent. Moreover, all four cases in which angioedema resulted in airway compromise occurred in subjects who began treatment with a 20 milligram starting dose, shown here. This analysis suggested that the incidence and severity of angioedema, particularly angioedema with airway compromise, might be reduced if patients were to begin therapy with a lower starting dose of omapatrilat.

The four cases of angioedema with airway compromise observed prior to OCTAVE are summarized here. All occurred in patients who had begun therapy with a 20 milligram starting dose. Two occurred on the first day of treatment, one on day 6 and one on day 11. All occurred while patients were receiving treatment with omapatrilat 20

milligrams prior to any dose titration. None of these cases presented in a fulminant manner; however, all required mechanical airway protection prior to resolution and all patients recovered without residual sequelae.

In the presentation that follows, I'm going to identify black race and current smoking as the two major risk factors for angioedema associated with omapatrilat, and one or both of these risk factors was present in 3 of the 4 subjects who experienced angioedema with airway compromise prior to OCTAVE.

Based on the observation that the incidence of angioedema appeared to be lower in patients who had begun therapy with doses of omapatrilat less than 20 milligrams, OCTAVE was designed in part to determine whether the incidence and severity of angioedema with omapatrilat could be reduced to a level comparable to that seen with ACE inhibitors if the starting dose of omapatrilat were reduced to 10 milligrams. Enalapril was chosen as a representative ACE inhibitor. And of note, the study wasn't designed to directly compare the incidence of angioedema with omapatrilat at starting doses of 10 and 20 milligrams.

Because of the difficulty encountered in previous studies in the accurate classification and counting of potential angioedema events, a special evaluation process was created for OCTAVE. Investigators

were actively solicited to report all potential angioedema events using a special case report form page, and then detailed follow-up information on each potential case was collected on a structured questionnaire to ensure a consistent and complete database. Potential angioedema cases were adjudicated by an expert committee without knowledge of treatment assignment. The analyses that follow are based on cases confirmed as angioedema by that expert committee.

As you know, angioedema occurred in 274 omapatrilat treated subjects, or 2.17 percent, as compared to 86 enalapril treated subjects, or .68 percent. And the relative risk of angioedema with omapatrilat versus enalapril was 3.17.

Corresponding to the scientific hypothesis that reduction in the omapatrilat starting dose would result in a rate of angioedema comparable to that of enalapril, a statistical hypothesis was prespecified in which a significant increase in the incidence of angioedema with omapatrilat relative to enalapril would be excluded if the upper bound of the 95 percent confidence interval for relative risk was less than 2. And clearly, this hypothesis was not confirmed, but nevertheless a fairly precise estimate of the relative risk of angioedema with omapatrilat relative to enalapril was provided with

reasonably narrow confidence limits.

An important secondary objective of OCTAVE was the assessment of the severity, as well as the incidence, of angioedema. Because no established classification systems for angioedema severity existed, a classification system was created for OCTAVE. Since it's not possible to obtain direct assessment of severity as these events occur, this system utilized treatment rendered as a proxy for severity.

The assignment of subjects to severity classes was performed by the event adjudication committee as part of their blinded review of angioedema cases. In this system, subjects receiving no treatment were assigned to severity class I, as were subjects treated only with antihistamines. Subjects treated with corticosteroids or epinephrine but not hospitalized were assigned to severity class II. Those who were hospitalized but did not require mechanical airway protection were assigned to severity class III, while subjects who required mechanical airway protection or subjects with fatal airway compromise were assigned to class IV.

It became apparent early in the trial that hospitalized patients were not consistently more ill than nonhospitalized patients treated with steroids or epinephrine and that at times patients were hospitalized

for observation or other reasons. As a result, we asked the adjudication committee to identify patients hospitalized with serious angioedema by determining if airway compromise was present and assigning patients to class IIIa or class IIIb accordingly.

As you know, in OCTAVE angioedema ranged in severity from mild and self-limited to life-threatening. No deaths occurred from angioedema in OCTAVE. The majority of patients, about 60 percent, who experienced angioedema with omapatrilat received no treatment or antihistamines only and were assigned to severity class I. One subject treated with omapatrilat experienced angioedema with airway compromise requiring mechanical airway protection and was assigned to severity class IV. A second omapatrilat treated subject experienced anaphylaxis with associated angioedema and transient airway compromise which resolved without mechanical airway protection, and this subject was assigned to severity class IIIb. No enalapril treated subjects angioedema with airway compromise. 17 omapatrilat treated patients and 2 enalapril treated patients were hospitalized for angioedema without airway compromise.

Analysis of the relationship between severity class and treatment group showed that patients who developed angioedema on omapatrilat had higher severity classes indicative of a more intensive treatment pattern

than those on enalapril. And in our review of the clinical manifestations of angioedema, we found that an appreciable difference between omapatrilat and enalapril events was the somewhat more frequent occurrence of tongue swelling and associated symptoms of difficulty speaking or swallowing with omapatrilat. And the more frequent occurrence of this highly symptomatic presentation may have led to this more intensive pattern of treatment.

Of greatest concern, of course, were the cases in which angioedema resulted in airway compromise. The rates of angioedema with airway compromise in OCTAVE and in all omapatrilat studies including OCTAVE are summarized in this slide. In OCTAVE, 2 patients, or 1.6 per 10,000 treated, experienced angioedema with airway compromise. If one places 95 percent confidence intervals around this rate, an upper confidence limit of 5.7 is seen, suggesting a rate of 6 per 10,000 as a worst case estimate. If one were to include all cases of airway compromise observed with omapatrilat, regardless of starting dose, a point estimate for the rate of angioedema with airway compromise would be 3.2 per 10,000 and the upper bound of the 95 percent confidence limit 7.0.

Now, it should be noted that the rate of angioedema with airway compromise observed in OCTAVE with the 10 milligram starting dose was distinctly different

from the rate of angioedema observed in prior studies with the 20 milligram starting dose. In OCTAVE, angioedema with airway compromise occurred in about 1 per 6,000 treated. In prior studies with the 20 milligram starting dose, angioedema occurred in about 1 in 600 treated.

While not definitive and not a direct comparison, these data do suggest that the rate of life-threatening angioedema is lower with the 10 milligram starting dose and that the estimate of angioedema risk obtained from OCTAVE is perhaps the most relevant estimate for considerations of benefit and risk based on the recommended dosing. But whether one uses the OCTAVE estimate or the estimate from the entire clinical development program, the worst case estimate that runs 6 to 7 per 10,000 is not meaningfully different.

The two cases of angioedema with airway compromise that occurred in OCTAVE are summarized here. The first occurred in a white female who developed edema of the eyelids, lip, and neck, difficulty speaking and swallowing, hoarseness, hypotension, and cyanosis within 15 minutes of the first dose of omapatrilat. This presentation with systemic manifestations, including cardiovascular collapse, as well as angioedema, within minutes of exposure to the drug is characteristic of anaphylaxis and was diagnosed as anaphylaxis by the

treating physicians. No other cases of anaphylaxis have been reported in the omapatrilat clinical development program. This subject was treated with epinephrine and recovered promptly. She was admitted to the hospital for observation and discharged the following day with no complaints.

A second case occurred in a black female during the 10th week of treatment with omapatrilat. She had been treated with omapatrilat 80 milligrams for about 4 weeks prior to the event without difficulty or dose interruption. Over a period of several hours, she developed diffuse and massive swelling of the face and oropharynx, as well as difficulty speaking and swallowing. She presented to the hospital emergency room within 2 hours of onset of symptoms and, about 3 hours after symptom onset, underwent tracheostomy for mechanical airway protection, and subsequently recovered completely.

Of note, both cases of angioedema with airway compromise in OCTAVE occurred in subjects with major risk factors for angioedema.

Now, 17 other omapatrilat treated patients and 2 enalapril treated patients were hospitalized for treatment of angioedema. Upon review by the adjudication committee, none of these patients were felt to have airway compromise. As discussed previously, many of these

patients had highly symptomatic and visible presentations of angioedema, including tongue and lip swelling, and in many cases angioedema was not the sole consideration in the decision to admit to hospital. None of these subjects had progression of their symptoms while in the hospital. 14 were discharged after 1 day, and 3 after 2 days in hospital. Thus, while the number of omapatrilat treated patients hospitalized for angioedema substantially exceeds the number of enalapril treated patients hospitalized for angioedema, the level of severity of these cases appears to be low.

Now, the rate of progression of angioedema, once it begins, is an important question. One case of anaphylaxis with associated angioedema was observed in OCTAVE, and this case progressed within a matter of minutes to a life-threatening condition. In general, as you've heard, angioedema that occurs outside of the syndrome of anaphylaxis progresses over hours rather than minutes.

To determine whether the rate of progression of potentially serious angioedema in OCTAVE with omapatrilat was consistent with that described for angioedema in other settings, we examined those cases that were considered serious enough to receive treatment with epinephrine or corticosteroids. We then characterized the length of time between the onset of symptoms and the receipt of treatment,

and since no treatment was received during that period, any progression would reflect the natural course of the episode. Other than the two cases with airway compromise discussed before, no patient had progression of angioedema to airway compromise.

And while about 20 percent of angioedema events treated with epinephrine or corticosteroids occurred in the doctor's office and therefore received immediate or near immediate medical attention, about 80 percent occurred outside of the physician's office. Of these, about two-thirds were associated with an elapsed time of at least an hour between the onset of symptoms and the patient's arrival at medical facilities, while in a substantial proportion of patients, more than 6 hours elapsed between the onset of symptoms and the patient arriving at medical facilities. The lack of rapid progression to airway compromise during the period from onset of symptoms to presentation at a medical facility is consistent with a rate of progression of the underlying disease measured in hours and not minutes.

A related question is whether angioedema with omapatrilat is sufficiently symptomatic and characteristic to be recognizable by the patient and prompt them to seek medical attention. In general, angioedema that might result in airway compromise is a highly symptomatic event

with visible and diffuse swelling. In OCTAVE, both patients who presented with angioedema and airway compromise were highly symptomatic with diffuse visible swelling and a constellation of other symptoms.

We examined the clinical presentation in all other cases to determine if there were any patients who presented with angioedema and potential airway compromise in an occult rather than clinically overt fashion. Perhaps the most worrisome presentation would be the patient who presented with nonspecific throat discomfort and no other signs or symptoms. In OCTAVE there were no patients who presented in this fashion. Every patient with angioedema had a clinically overt presentation with visible swelling. Many had accompanying functional complaints, such as difficulty swallowing or difficulty handling oral secretions attributable to the swelling, and no patients with angioedema had nonspecific lower airway complaints such as stridor, dyspnea, or hoarseness alone.

The time course of angioedema with omapatrilat is illustrated here. The risk is greatest during the initiation of therapy. 88 cases, about one-third of all cases, of angioedema with omapatrilat occurred on the first day of treatment, as opposed to only 3 cases on the first day of treatment with enalapril. Many of these occurred within 2 hours of administration of the first dose.

Nevertheless, angioedema continued to occur although at much lower rates through the trial. In the last weeks of the trial, the rate of angioedema was low with both drugs, though still about twice with omapatrilat compared to enalapril. Based on the observed incidence of angioedema in the last weeks of OCTAVE, one might predict that the rate of angioedema of any degree of severity during chronic treatment to be about 1 or 1.2 percent per year.

Now, data from studies prior to OCTAVE identified two potential risk factors for developing angioedema with omapatrilat: black race, which has also been described as a risk factor for ACE inhibitor-associated angioedema, and smoking.

An exploratory analysis of the OCTAVE data was performed to determine the effect of demographic characteristics, comorbidities, treatment history, and personal habits on the risk of angioedema with omapatrilat. The results of these analyses are summarized in this figure. On the left, is the multivariate relative risk of angioedema with omapatrilat in subjects with the stated characteristic compared to those without those characteristics. For example, the relative risk for angioedema in omapatrilat patients who currently smoke is 2.58 times that seen in patients who never smoke. On the right side is the observed incidence of angioedema in

patients with these stated characteristics.

These analyses confirmed the importance of black race and smoking as risk factors for developing angioedema with omapatrilat. These two characteristics were associated with at least a doubling in risk of angioedema shown here, and the observed incidence of angioedema in these patients was 5.5 percent in black patients and 3.9 percent in current smokers.

Several other characteristics shown here, not identified as potential risk factors in the prior database, were found to be associated with either modest increases or modest decreases in the risk of angioedema. Of note, while it was expected that a history of treatment with and tolerance of ACE inhibitors might be associated with decreased risk of angioedema, this was not observed.

In sum, through an extensive clinical development program, the safety of omapatrilat has been very well characterized. This program has identified an incremental risk of angioedema relative to ACE inhibitor treatment which must be weighed against the potential benefit of greater blood pressure reduction.

With omapatrilat, as in other clinical settings, angioedema has a wide spectrum of severity. Current smokers and black patients have been shown to have a substantially higher risk.

In OCTAVE, the rate of life-threatening angioedema was 1.6 per 10,000 patients treated, and the upper bound of the 95 percent confidence interval for this estimate was about 6 per 10,000.

With omapatrilat, as in other clinical settings, angioedema was a symptomatic event with a characteristic presentation. In those with severe symptoms, the rate of progression was rapid but not fulminant, and all patients who developed angioedema with omapatrilat were successfully treated.

Bristol-Myers Squibb has proposed a risk management plan for omapatrilat that would minimize the risk of life-threatening angioedema through a comprehensive system of education. As I've noted, angioedema is a condition with clinical features which facilitate its management through education. It has a symptomatic and recognizable clinical presentation, rapid but not fulminant progression, and effective therapy can help to prevent poor outcomes.

The objective of the plan is to ensure a favorable benefit-risk ratio for patients taking omapatrilat. The cornerstone of the plan is a multifaceted and comprehensive program of education for prescribers, pharmacists, and patients. The approved labeling and other educational modalities will be used to educate physicians