FOOD AND DRUG ADMINISTRATION

NINETY-SEVENTH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUG ADVISORY COMMITTEE

8:01 a.m.

Thursday, July 18, 2002

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

ATTENDEES

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ATTENDEES (Continued)

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CINDY M. LANCASTER, M.S., M.B.A., J.D.
ERIC MICHELSON, M.D., F.A.C.C.
VASILIOS PAPADEMETRIOU, M.D., D.SC., F.A.C.C.

BRISTOL-MYERS SQUIBB REPRESENTATIVES:

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TODD BAUMGARTNER, M.D.
RENE BELDER, M.D.
BERNARD R. CHAITMAN, M.D.
LAWRENCE J. DACEY, M.D.
FRED FIEDOREK, M.D.
CHARLES H. HENNEKENS, M.D., DR.PH.
THOMAS A. PEARSON, M.D., PH.D., M.P.H.
ERIC J. TOPOL, M.D.

C O N T E N T S

MORNING SESSION

* * *

NDA 20-838/S015, Atacand (candesartan cilexetil) Tablets,
AstraZeneca LP,
For a Proposed Claim of Comparative Efficacy of
Candesartan Cilexetil and Losartan in Hypertension

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C O N T E N T S

AFTERNOON SESSION

* * *

NDA 21-387, Pravastatin/Aspirin Combination Product,
Bristol-Myers Squibb Company,
Proposed for Long-term Management to Reduce the Risk of Cardiovascular Events (death, nonfatal myocardial infarction, myocardial revascularization procedures, and ischemic stroke) in Patients with Clinically Evident Coronary Heart Disease

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P R O C E E D I N G S

(8:01 a.m.)

DR. BORER: It's 8:01 and 57 seconds, so we're already a minute and 57 seconds late. I'd like to call this meeting to order so we can catch up.

We'll begin by introducing the committee members, and we'll start over on the left side with our guest committee member, Tom Pickering, who is a nonvoting member for this particular meeting. Tom, why don't you give your name, your affiliation, and we'll go around the table.

DR. PICKERING: I'm Dr. Tom Pickering and I'm Professor of Medicine and Director of the Integrative and Behavioral Cardiovascular Health Program and Hypertension Section at Mount Sinai School of Medicine in New York.

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

DR. NISSEN: I'm Steve Nissen and I'm Vice Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic School of Medicine.

DR. ARMSTRONG: Paul Armstrong, cardiologist, professor of medicine, University of Alberta.

DR. BORER: I'm Jeff Borer from Cornell Medical College.

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

acting Executive Secretary of the Advisory Committee.

DR. FLEMING: Tom Fleming, University of Washington, Seattle.

DR. LINDENFELD: JoAnn Lindenfeld, University of Colorado.

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

DR. LORELL: I'm Beverly Lorell from Harvard Medical School and Beth Israel Deaconess Medical Center.

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

DR. BORER: Alan Hirsch, a regular member of this committee, will not be here today. I believe that Susanna will be here, but she's not here yet.

This seems a good time to remind everybody that if you want to say something, please press your button so I can see the light and everybody can hear you.

We'll have the conflict of interest statement from Jayne Peterson, the acting Executive Secretary of the committee.

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 a competitor to Atacand 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 Atacand. The stock is valued between $25,000 and $50,000.

Dr. JoAnn Lindenfeld has been granted a waiver under 18 U.S.C. 208(b)(3) for her potential consulting for the sponsor and competitors to Atacand on unrelated matters. Potentially she could receive less than $10,001 from each firm per year and for her speaking for the sponsor and competitor to Atacand on unrelated matters for which she receives greater than $10,000 per year.

Dr. Thomas Fleming has been granted a waiver

under 18 U.S.C. 208(b)(3) for his participation on a data safety monitoring board for a competitor to Atacand on a related matter. He receives less than $10,000 per year.

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.

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: Thank you.

We'll begin then with the presentation by the sponsor of the proposed amendment to the NDA for candesartan cilexetil tablets. We'll begin with Dr. Lancaster.

MS. LANCASTER: Good morning, Mr. Chairman, members of the committee, members of FDA, and ladies and

gentlemen. My name is Cindy Lancaster from the Department of Regulatory Affairs at AstraZeneca. On behalf of AstraZeneca, I would like to thank the division and the committee for giving us the opportunity to present the results of our clinical program about the antihypertensive efficacy of candesartan cilexetil compared to losartan.

I'm presenting a brief regulatory overview this morning. Following the regulatory overview, Dr. Papademetriou will present the results of our clinical program on the antihypertensive efficacy of candesartan cilexetil compared with losartan. Dr. Kannel will then present the epidemiologic and the clinical significance of incremental changes in blood pressure. Following Dr. Kannel's presentation, I will provide a brief summary.

In addition to Drs. Kannel and Papademetriou, Dr. Donald Vidt is also a consultant for AstraZeneca on the CLAIM program. Dr. Vidt was the principal investigator for study 230 and the primary author of the publication describing this study. Other members of the AstraZeneca team who are identified on this slide are also available to address specific questions that the committee or FDA may have this morning.

Atacand is a selective AT1 subtype angiotensin II receptor antagonist. This product belongs to the class known as the angiotensin receptor blockers and this class

is commonly referred to as ARBs.

Atacand was approved in June 1998 by FDA for the treatment of hypertension. Atacand can be used alone or in combination with other antihypertensive agents for the treatment of hypertension. The usual recommended starting dose is 16 milligrams once daily, and this product can be administered once or twice daily with total daily doses ranging from 8 to 32 milligrams.

Study 01, the first comparator trial, is one of the 14 placebo-controlled trials included in the original NDA database that formed the basis of FDA's approval of Atacand for the treatment of hypertension in 1998. Study 01 was a randomized, double-blind, multicenter, placebo-controlled, parallel group, 8-week comparator study of 8 and 16 milligrams of candesartan cilexetil, 50 milligrams of losartan, another product in the ARB class, and a placebo given once daily. A total of 337 patients with a mean sitting diastolic blood pressure of 95 to 114 millimeters of mercury were randomized to one of four parallel treatment groups.

With only a single study of a comparison at the starting dose available at the time of the FDA's review of the NDA database, AstraZeneca did not propose any comparator text in the labeling based on the positive results of this trial at that time.

However, a second study was ongoing at the time of FDA's review of the original NDA. Results of the second positive study became available later in 1998. This was a trial conducted in the U.S. It was a randomized, double-blind, multicenter titration-to-effect, 8-week study with parallel treatment groups of candesartan cilexetil initiated at 16 milligrams once daily compared with losartan initiated at 50 milligrams once daily.

There were 332 patients with a mean sitting diastolic blood pressure of 95 to 114 millimeters of mercury randomized to two parallel treatment groups.

Since this study was a titration-to-effect design, patients with a mean sitting diastolic blood pressure of greater than or equal to 90 millimeters of mercury after 4 weeks of initial treatment were titrated to either 32 milligrams of candesartan cilexetil or 100 milligrams losartan once daily.

Because the results of study 175 were available in August 1998, AstraZeneca met with representatives from the Division of Cardio-Renal Drug Products, the Office of Drug Evaluation I, and DDMAC to discuss the possibilities of study 01 and 175 supporting a comparator claim of Atacand versus losartan. Although each study met its primary endpoint, the agency commented that study 01 did not provide a meaningful comparison because the starting

dose is an arbitrary point in the dosing regimen and it does not reflect how the drugs being compared would actually perform over their dose ranges.

In addition, the agency noted that the design of study 175 was not a forced titration study. Consequently the agency expressed some concern that in a titration-to-effect study only the poor responders would be titrated to the highest dose of the drugs.

Following this meeting and in subsequent discussions, the agency asked AstraZeneca to establish the bioequivalence of the overencapsulated losartan tablet to the commercial product. The overencapsulation was done for blinding purposes. In response to this request, AstraZeneca designed and conducted a bioequivalence study. The study established the bioequivalence of the test drug, losartan, used for the comparator studies conducted by AstraZeneca.

AstraZeneca was also asked to focus on the maximum approved of the comparator drugs, demonstrate the statistical significance with two adequate and well-controlled trials, and if only once-daily dosing is studied, then the limitations should be clearly stated in promotional claims, as well as the study design needed to be either a parallel dose-response or a forced-titration.

Now, based on these requirements, AstraZeneca

designed and conducted the CLAIM program entirely in the U.S. The results of a specific dosing regimen of once-daily administration that was used in the CLAIM program is described in our proposed labeling. AstraZeneca selected the once-daily dosing regimen for candesartan cilexetil and losartan because both drugs are prescribed for use once daily, and once-daily administration is the dosing regimen primarily used in completed and ongoing studies.

Statistically greater blood pressure reduction was demonstrated with candesartan cilexetil compared with losartan at the maximum approved dose when administered once daily.

The proposed labeling is specific to effects on blood pressure reduction.

Now, based on the results of the CLAIM program, AstraZeneca proposes the following text be added to the labeling in the clinical pharmacology section within the clinical trials subsection of labeling after the first paragraph within our approved labeling.

"Two identically designed, concurrently conducted, 8-week, multicenter, double-blind, randomized, forced-titration studies were performed to compare the antihypertensive efficacy of candesartan cilexetil and losartan at their once-daily maximum doses. Candesartan cilexetil initiated at 16 milligrams once daily and forced-

titrated at 2 weeks to 32 milligrams once daily was statistically significantly more effective than losartan 50 milligrams once daily forced-titrated at 2 weeks to 100 milligrams once daily in reducing systolic and diastolic blood pressure at 8 weeks. In these studies, both agents were well tolerated."

This proposed text would be included in the clinical trials section in the context of our approved indication and usage section of labeling which states: "Atacand is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents."

Now, during the course of the review of our supplement, the FDA also asked us about precedents for comparator and superiority labeling in other antihypertensive products. We provided several, which are described in the background information document, and many of these labels make the claim of similar efficacy. I will review the example of this comparator information found in labeling for you this morning, at least one example that we have, which is lisinopril which is marketed under the trade names of Zestril and Prinivil, and it has a superiority claim within the clinical pharmacology section of its labeling. It states that 20 to 80 milligrams of lisinopril was superior to hydrochlorothiazide in the effect on

systolic and diastolic blood pressure and it was equivalent to atenolol and metoprolol in effects on diastolic blood pressure.

In summary, AstraZeneca's proposed labeling is consistent with the general requirements of the content and format for human prescription drugs. This proposal is also consistent with the guidance from FDA on how these studies should be described in the labeling, and a review of other approved antihypertensive products confirms that our proposed labeling is consistent with the content and placement of comparator information in labeling. More specifically, our proposed labeling is consistent with the labeling for lisinopril and losartan, as well as other antihypertensive products such as the ACE inhibitors, Accupril, and Altace, and the other ARBs, Diovan and Teveten. Consequently, AstraZeneca proposes that this information be included in the labeling for Atacand.

At this time, please allow me to introduce Dr. Papademetriou who will present the results of our clinical program on the antihypertensive efficacy of candesartan cilexetil compared to losartan.

DR. BORER: Are there any specific substantive questions for Dr. Lancaster, or can we move right ahead?

(No response.)

DR. BORER: Okay, thank you very much.

DR. PAPADEMETRIOU: Good morning, everyone. It is a pleasure to be here and I appreciate this opportunity to present to you the comparative data of two angiotensin receptor blockers, candesartan cilexetil and losartan.

This morning I would like to present data from the CLAIM program which consists of two identical, well-controlled clinical trials, studies 230 and 231.

First, let me begin with this slide just to refresh everyone's memory of the cascade of the renin-angiotensin system that lists the production of angiotensin II. As we all know, angiotensin I is produced by angiotensinogen through the activity of renin, and angiotensin I is transformed into angiotensin II through the activity of the angiotensin-converting enzyme. The same enzyme is responsible for the breakdown of bradykinin through inactive ingredients. This is the site where ACE inhibitors exert their activity and decrease the production of angiotensin II. At the same time, levels of bradykinin increase and this has been implicated as the cause of some of the side effects of ACE inhibitors such as cough and angioneurotic edema.

Angiotensin II can also be produced by pathways that do not use the angiotensin-converting enzyme. This is why sometimes angiotensin II can return to its baseline after administration of ACE inhibitors. By stimulating the

AT1 receptor, angiotensin II produces all the effects of the activated renin-angiotensin system such as vasoconstriction, fluid and sodium retention, sympathetic activation, and in the long-term self-proliferation and vascular hypertrophy, all of which lead to the development of hypertension.

Angiotensin receptor blockers accept their activity directly at the receptor site and prevent activation by angiotensin II.

Because previously published experimental data suggested that the binding properties of candesartan were different than losartan, studies were designed to assess whether this observation translates into clinical differences in blood pressure lowering.

Here we present data from two of these studies, 001 and 175. Both were randomized, double-blind, multicenter, controlled, parallel group studies. Both clinical trials were of 8-week durations and were conducted in patients with diastolic pressures of 95 to 114.

In study 001, 337 patients were randomized to four treatment groups: candesartan cilexetil 8 milligrams; candesartan 16 milligrams; losartan 50 milligrams; or placebo.

In study 175, 332 patients were randomized to receive candesartan cilexetil 16 milligrams or losartan 50

milligrams.

If after 4 weeks, the diastolic blood pressure was not below 90 millimeters of mercury, the dose of candesartan cilexetil was increased to 32 milligrams and that of losartan was increased to 100 milligrams.

Here are the results of studies 001 and 175. As you can see, in study 001, the placebo-corrected reduction in blood pressure was approximately 10.3 millimeters of mercury with candesartan cilexetil 16 milligrams, and approximately 6.6 millimeters of mercury with losartan 50 milligrams. That resulted in a difference of 3.7 millimeters of mercury which was statistically significant.

In study 175, there was a reduction of approximately 11 millimeters of mercury with candesartan and 8.9 millimeters of mercury with losartan, a mean difference of 2.2 millimeters between the two treatment groups which was also statistically significant.

The CLAIM program was specifically designed to assess the effect of two angiotensin receptor blockers, candesartan cilexetil and losartan, in blood pressure lowering in hypertensive patients. The program included two identically designed studies, studies 230 and 231. In these trials the maximum recommended dose of each agent administered once daily, as described in the respective

approved labeling of each drug, was used in a forced-titration design. This means that the higher dose was administered to patients even though their diastolic pressure might have been a target with the lower dose administered.

Eligible patients entered in a placebo run-in period for 4 to 5 weeks and were then randomized to receive either candesartan 16 milligrams or losartan 50 for 2 weeks. Subsequently the dose was increased to candesartan 32 milligrams or losartan 100 milligrams for an additional 6 weeks. The total treatment period, therefore, was 8 weeks, at the end of which blood pressure measurements were taken 24 hours after the last dose. To simulate the possibility of a missed dose, measurements were also taken 48 hours after the last dose was administered.

Eligible patients for these trials were between the ages of 18 and 80. They were male patients or females without child-bearing potential or using appropriate birth control measures. They had to have essential hypertension as patients with secondary causes were excluded, and a mean diastolic pressure between 95 and 114 on two consecutive visits at the end of the placebo run-in period. Patients were excluded from the study if they had one or more of the exclusion criteria listed on this slide. These are the common exclusion criteria used in most hypertension trials.

The primary endpoint was the change from baseline to week 8 in trough sitting diastolic blood pressure. A number of predefined secondary endpoints were also assessed and these included change from baseline to week 8 in trough sitting systolic pressure, change in peak diastolic and systolic pressure, the trough-to-peak ratio, the proportion of patients considered controlled or responders, and the change in systolic and diastolic pressure at 48 hours post the last dose.

Now, let me clarify some of the terms used in the CLAIM program. Trough and peak drug effects, as stated in the approved label of both drugs, were defined as follows. The trough effect was considered the effect at 24 hours post dose, and the peak drug effect was considered the effect at 6 hours post dose. Patients with a trough diastolic pressure below 90 were considered controlled, and patients were considered responders if they either had diastolic pressure below 90 or at least they had demonstrated a 10 millimeters of mercury reduction from their baseline diastolic blood pressure.

The primary statistical analysis was performed using an analysis of covariance, ANCOVA, for the change from baseline to week 8 in trough sitting diastolic blood pressure. The primary patient population was an intent-to-treat population where patients had to have a baseline and

at least one post-baseline blood pressure measurement. An analysis using the last observation of treatment carried forward, or LOCF, was also performed to account for missing values.

The ANCOVA model included a treatment, center, and center-by-treatment interaction, and baseline diastolic pressure was a covariate to account for potential baseline differences.

The differences between treatments are presented as least squares means.

The sample size calculation was based on detecting a difference of 2 millimeters of mercury between treatment groups, a standard deviation of 7.5 millimeters of mercury, a significance level of 0.05 for a two-tailed test, and a power of 95 percent. This resulted in a sample size calculation of 735 patients for each study. However, 613 patients and 655 patients were randomized to study 230 and 231, respectively.

In study 230, a total of 926 patients were screened, of which 613 patients qualified for the study. Of those, 309 patients were randomized to receive candesartan cilexetil and 304 were randomized to receive losartan. Of the 309, patients 2 patients were discontinued without post-baseline contact and 307 patients formed the intention-to-treat population for candesartan

cilexetil. In the losartan group, 304 patients were randomized. All of these patients had post-baseline contact and formed the intention-to-treat population. Approximately 12 percent of patients were discontinued from each treatment group.

Similarly, in study 231, out of 921 patients screened, 655 were randomized: 332 to candesartan and 323 to losartan. All patients randomized to candesartan cilexetil had post-baseline contact and were considered the intention-to-treat population. In the losartan group, of the 323 patients, 1 patient had no post-baseline contact and was discontinued from the study. 322, therefore, formed the intention-to-treat population. In this study, 4 to 6 percent of patients were discontinued from each treatment group for various reasons.

The baseline characteristics were similar between the candesartan cilexetil and the losartan treatment groups in both studies. Patients were similar in age, weight, duration of hypertension, sex distribution, and race. Approximately 18 to 20 percent of patients in each study were African Americans.

Baseline blood pressure was also similar for both treatment groups and diastolic pressure averaged around 100 millimeters of mercury and systolic blood pressure ranged between 152 and 153 for all groups

randomized in the two trials.

The primary endpoint, that is, the change in diastolic blood pressure at week 8, is shown on the left for study 230. In this study, patients receiving candesartan cilexetil had a mean diastolic blood pressure reduction of 10.5 millimeters of mercury, whereas patients receiving losartan had a 9.1 millimeters of mercury reduction in trough diastolic blood pressure. This resulted in a statistically significant difference of 1.5 millimeters of mercury between the two treatment groups.

In study 231, shown on the right, candesartan cilexetil therapy resulted in an average diastolic pressure reduction of 10.9 millimeters of mercury. Treatment with losartan resulted in an average pressure reduction of 8.7 millimeters of mercury. The difference between the two treatment groups was 2.2 millimeters, and this was also statistically significant.

The primary endpoint is shown here, together with a number of secondary endpoints, for study 230. As you can see, there is a 3.4 millimeters of mercury greater reduction in trough systolic blood pressure, a 3.4 millimeters greater reduction in peak diastolic blood pressure, and a 3.5 millimeters greater reduction in peak systolic blood pressure. At 48 hours after the last dose, the difference between the two groups was maintained and

was 2.8 for diastolic and 4.6 millimeters of mercury for systolic blood pressure. For all primary and secondary endpoints, differences between candesartan cilexetil and losartan were statistically significant.

Similarly in study 231, statistically significant differences were noted: 2.2 millimeters of mercury change in the trough diastolic pressure, 3.5 millimeters for trough systolic blood pressure, 1.5 and 2.6 for the peak diastolic and systolic blood pressure, respectively. And at 48 hours, the differences were again statistically significant in favor of candesartan with a mean change of 4.3 and 5.9 millimeters of mercury in diastolic and systolic blood pressure, respectively.

This slide shows the trough diastolic blood pressure reduction during therapy by visit for studies 230 and 231.

In study 230, there was a substantial decrease in diastolic blood pressure with both agents after 2 weeks of therapy, but the reduction was greater with candesartan cilexetil. After up-titrating the dose, further blood pressure reduction was noted with both drugs, but the difference between candesartan cilexetil and losartan was maintained for the duration of the study.

Similarly in study 231, there was an initial substantial reduction of diastolic blood pressure with both

agents, but the blood pressure reduction was greater with candesartan cilexetil at 2 weeks of therapy. After up-titrating the dose, a further blood pressure reduction was noted and the difference was again maintained for the duration of the study.

Similar results were obtained for systolic blood pressure in both studies, 230 and 231. Differences between candesartan cilexetil and losartan were observed after 2 weeks of therapy and were maintained after up-titration for 8 weeks. In study 230, although the mean baseline systolic pressure was slightly higher in the candesartan group, the blood pressure reduction was greater and was maintained for the duration of the study.

The trough-to-peak ratio is an important measure because it indicates the duration of blood pressure lowering action of the medication used. The trough-to-peak ratio was a prespecified secondary endpoint in these studies. As you can see here, in both studies 230 and 231, the trough-to-peak ratio for candesartan cilexetil and losartan was close to 0.9. This indicates that the blood pressure lowering effect of both drugs is well maintained over a 24-hour period with once-daily dosing.

This slide shows the percent of patients that were considered either controlled or responders in the two studies. As you can see, numerically the numbers of

controlled patients or responders for each therapy was greater with candesartan cilexetil in both studies. The differences achieved statistical significance in study 231.

This slide shows the blood pressure differences between the two therapies in the overall population and in prespecified subpopulations of studies 230 and 231, as well as the pooled data. Although these studies were not powered to assess the effects in subpopulations, the results are consistent with the overall effect.

Here are the results for systolic blood pressure reduction in the same subpopulations and reductions in systolic pressure were also consistent with the overall outcomes in both studies 230 and 231 and the pooled data.

The summary of adverse events reported in the CLAIM program is consistent with adverse events reported in most hypertension trials. Most events were mild and transient in nature. The number of patients that reported at least one adverse event was similar between treatment groups. About 46 percent of the patients in the pooled data reported at least one adverse event. Serious adverse events and events requiring discontinuation from the study were infrequent.

Adverse events reported in more than 2 percent of patients are shown here. In general, these events were

similar between the two treatment groups, were transient and rarely led to discontinuation from the study.

In summary, the efficacy data from the two CLAIM studies indicate that the reduction in blood pressure was consistently in favor of candesartan in both studies. Differences in trough diastolic and systolic blood pressure and peak diastolic and systolic pressures were consistently greater for candesartan compared to losartan.

If we add to these studies the primary endpoint data for studies 175 and 001, again we can see that reductions in trough diastolic pressure were consistently in favor of candesartan.

In summary, the CLAIM program, which included two adequate and well-controlled studies, provides substantial evidence that treatment with candesartan cilexetil results in greater blood pressure reduction compared with losartan at the maximum recommended doses administered once daily.

Furthermore, candesartan cilexetil 32 milligrams once daily consistently lowered trough, peak, and 48-hour post-dose diastolic blood pressure and systolic blood pressure more effectively than losartan 100 milligrams daily.

Both drugs were well tolerated and demonstrated a tolerability and safety profile consistent with current

prescribing information.

In conclusion, the greater blood pressure lowering effect of candesartan cilexetil compared with losartan in the two CLAIM studies is consistent with other studies that were conducted previously. This information is clinically relevant and important for prescribing health care professionals.

Thank you very much.

DR. BORER: Thank you, Dr. Papademetriou.

I'm sure there are a number of questions from the committee about substantive issues. We'll get into the interpretation issues later, but I'd like to begin with just a few questions about the conduct of the trials, and these aren't meant as criticisms in any way. I just want to understand how the data were collected.

First of all, do we have any idea within the primary study populations, or any subpopulation within them, of the distribution of renin sodium profile data for these patients?

One of the reasons I ask the question is that in 230 the very small subpopulation of black patients showed no effect of treatment; in 231 they did. I don't want to belabor small subset analyses that weren't primarily hypothesized to be done in the first place, but the fact is that one might expect that black patients would

be less likely to respond to ARBs or ACE inhibitors than white people would. And that raises the issue of renin sodium profile. So, just for my information, do we have any data about that?

DR. PAPADEMETRIOU: No, unfortunately, these data were not collected in these studies.

DR. BORER: Okay.

How about the time at which the blood pressure measurements were made? I understand they were done at trough and at peak, and that that pretty well sets a window around the timing of the determination of blood pressure. But were they predominantly or solely done in the morning for the trough, or were they done some in the morning, some in the afternoon for patient convenience?

DR. PAPADEMETRIOU: Almost all patients had their measurements in the morning time.

DR. BORER: Let's see. A couple of other little questions. Oh, yes. The weight of the patients. These were pretty heavy patients on average. The women, as I recall, in all the study populations averaged somewhere around 185 pounds per person. I know there was a wide distribution of weights, but can you comment, first of all, on the distribution of weights in the general hypertensive population so that we can know whether this is really a reasonable microcosm and on what the impact of weight may

have been here?

DR. PAPADEMETRIOU: This is a very good point, and the body mass index turned out to be over 30 in about half of the patients in these study populations. But from what I know from epidemiology data, that reflects pretty much what happens around the country.

DR. BORER: The other issues that I would raise are actually qualitative or more appropriate for Dr. Kannel. Let's go on to Paul as the committee reviewer. Do you have some specific issues you want to raise?

DR. ARMSTRONG: Thank you. I do. I will come to a specific table in the briefing document in a moment that I would like your advice on. But I really have three questions to begin with, actually based on the chairman's question, perhaps a fourth, which I'll just put up front.

Given the spectrum of weight, do we have any information about efficacy when you correct for weight? In other words, was there more of an effect in patients with a low body weight than those with a high body weight? Do we know that?

DR. PAPADEMETRIOU: We do have the response in the obese compared to non-obese, and I can show that to you if you like. As you can see here, the blood pressure reduction of diastolic blood pressure overall in the obese and non-obese was pretty similar. The obese patients

pretty much had the same response in diastolic pressure and similarly in the systolic blood pressure too.

DR. ARMSTRONG: Thank you.

There are really three issues then that I think we'll come back to. One is the evidence to support incremental effect at doses of candesartan above 16 and losartan above 50. So, I'd like your comments about the evidence supporting increased efficacy above those doses.

The second is the time course to stable effect when you begin with once-a-day dosing as one looks at the time course and when a steady state is reached and the evidence to support a difference in the time course with candesartan versus losartan, given the comments about the difference in the duration in receptor activity of the two drugs.

And the third is the evidence to support b.i.d. dosing versus once-a-day dosing enhancing effect in one versus the other compound.

Those three issues to me come through repetitively. Can you comment on those? And then I'd like to direct your attention to a specific table in the briefing document.

DR. PAPADEMETRIOU: These data are available. We didn't have time to present them here, but Dr. Michelson probably would be more appropriate to answer these

questions.

DR. MICHELSON: Hi. Good morning. Dr. Eric Michelson, AstraZeneca. Let me just help with a few of these, if I can.

Dr. Armstrong, if I understood correctly, the first question had to do with the time course of perhaps stabilization with respect to once-a-day dosing.

DR. ARMSTRONG: Yes, and if you like, we can work with that and the table in the briefing document that I think addresses that also, but please go ahead.

DR. MICHELSON: I think when we designed these studies, we were, to the best of our ability, trying to be as consistent with the prescribing information for the label of both drugs, and for each of the drugs, it's stated that these drugs reach their maximum effect within either 2 to 4 weeks or 4 to 6 weeks. In fact, for losartan it's 2 to 4 weeks, and we state in our label 4 to 6 weeks. So, the studies were designed with the idea in mind that a 6-week at a stable dose would be sufficient.

DR. ARMSTRONG: Well, to that point, on page 6 of the briefing document which addresses the CANDLE study, there is a table which then partitions the patients who were up-titrated in the lower part of that panel and not up-titrated in the upper panel. It looks to me as though, as one looks at the patients who were not up-titrated, that

indeed there is a further effect, as you have implied, between week 2 and week 4; that is to say it does appear, though, by week 4 that the blood pressure lowering effect stabilizes.

That being the case, then the patients who were then up-titrated based on measurements at 2 weeks, it's impossible for me to discern the notion that at 4 weeks that effect relates to an increment in the dose as opposed to an elapsing of the time. That obviously is a key point. I wonder if you can shed light on that.

DR. MICHELSON: Yes. Let me try to help clarify. The way it's depicted in the briefing document may not add clarity. The design of the study, the CANDLE study 175, was actually titration to effect where the titration was at week 4. The way it's presented in the briefing document, the review by Dr. Fred, suggests that it's at week 2, but it was actually done at week 4. So, there were incidental blood pressure measurements collected, merely incidental, at weeks 2, 4, 6, just to watch the traffic as it was going by. But the only decision about up-titration was made at week 4.

DR. ARMSTRONG: So, the week 4 measures here --

DR. MICHELSON: Were the sole basis for up-titration.

DR. ARMSTRONG: So, in the patients who were

up-titrated, the week 4 measurements were before the up-titration. Is that correct? I'm a little confused.

Can you comment then on the issue of evidence for incremental effect beyond 16 milligrams and why starting at 16, given that there's substantial evidence that 8 in some of the other material is effective? Why start at 16?

DR. MICHELSON: Let me just comment first that 175, in part, reflects as clinicians what we would probably routinely do. The usual recommended starting dose for each of these drugs is respectively 50 milligrams and 16 milligrams, and in the population being study, nonhepatically impaired, whatever, this would be the appropriate starting dose. In fact, that's the way the study was designed and then it was titration to effect.

In this study, the question that was being directly asked for us was to address the maximum doses. When we discussed this with Dr. Temple, our understanding was it would have been completely acceptable in this study, the way this experiment would have been designed, we could have just started with 32 milligrams and started with 100 milligrams. And that would have satisfied the question whether or not at the maximum recommended doses administered once daily was there a difference.

And in designing the study, we suggested that

perhaps just to make it a little bit more comfortable for the clinicians doing the study for them to have the opportunity to then put in an opportunity to start at a lower dose. There wasn't even a question about how long that could have been. Dr. Temple even said it could have been 2 days if we wanted, but we decided to make it, again, just more in tune with clinical practice, 2 weeks.

We would never be recommending on a routine basis that 2 weeks would be an adequate time necessarily to fully evaluate the effect of any dose, whether it's 8, 16, or 32. In fact, the whole analysis was really concentrated on what happened at week 8. This was just an instrument to be able to get the patients up to 32 and 100.

DR. ARMSTRONG: Thank you.

Then the final question I have at this point relates to whether there is evidence to support b.i.d. dosing is indeed more effective than once-a-day dosing with candesartan as opposed to the implication for losartan.

DR. MICHELSON: Yes. Let me see if I can help you here. There is a slide. I believe it's CS-34. Why don't you take a look and see if that's it. But it's a study by Zuschke, study 116. Let me share this with you.

By the way, the slide we never got to discuss a moment ago in fact addressed whether or not there was evidence for a dose response above 16 milligrams. So, if

you wanted to get back to that, they know where they slide is. I'll be happy to discuss it with you. Okay?

But if you're asking whether there's any evidence at all, a study was done, placebo-controlled trial, looking at 8 milligrams twice daily versus 16 milligrams once daily, and at these doses you can see that the study had 90 patients per arm. It wasn't powered to look for relatively smaller differences, but as you can see, there are differences of the order of about 1.7, 1.8 millimeters of mercury for systolic blood pressure and differences of the order of about 1 millimeter of mercury for diastolic blood pressure.

DR. ARMSTRONG: But coming back to your request for a label change and the issue of whether losartan administered twice daily would be as effective or more effective than candesartan once daily, would you say that the evidence for losartan b.i.d. is better in terms of efficacy than the b.i.d. data that you're showing us for candesartan?

DR. MICHELSON: If I can, let me address something which is a similar type of piece of information which we have for losartan. It's a study that actually Dr. Weber did. Let me see if I can help you out here. Actually Dr. Weber did this for Merck, not for us.

This is a small piece of a more elaborate study

that he did. I apologize to Dr. Weber, without his permission, for taking this out of context, but just to address your specific question, when losartan was looked at -- and all this is now, again, this is sitting diastolic blood pressure at the end of a 4-week period. That was the way Merck designed the study looking at 100 milligrams once daily versus losartan 50 milligrams b.i.d., and it's the only information I could find on the use of 50 b.i.d. There's no other information I could find in the literature. In this study, you can see again the difference between those two in diastolic blood pressure is a very, very similar order of magnitude.

DR. THROCKMORTON: Paul, just to remember, that was commented on in the FDA briefing document too I think on page 14. Dr. Fred had looked at some other materials as well.

DR. MICHELSON: And about the doses, there's one other slide I wouldn't mind showing if we can get it. Would you like to look at the dose response for either candesartan or losartan? Would that be of interest or not?

Could we go back to the Rife slide?

DR. BORER: Before you begin speaking about it, Eric, Bob, you had a comment?

DR. TEMPLE: Just a comment. As a matter of general policy, if the b.i.d. versus o.d. comparisons that

we usually see at least a little data for even sort of lean towards suggesting that b.i.d. might be better, we say maybe b.i.d. will be better. One doesn't want to treat those rigorously. Obviously, to validate the kinds of differences we're talking about, you need studies of the same size that were done here, and that is quite unusual. So, like many dose response things, we look at the numbers and write down the descriptive data. These are not rigorously statistically meaningful differences. The impression we had was that there might be some small advantage to going b.i.d. if you didn't get where you wanted, and you could try it.

DR. BORER: I'd like to interject one minor point here as well. I think that Paul's question is very important. We'd like to know the optimal dosing regimen for any of these drugs. They probably should appear in the label or what we know about them should.

Even though our decisions aren't based on medical economics, I think it's important to recognize that it's very useful to have the q.d. information nonetheless because third party payors are now, in many cases, refusing to pay for drugs for their clients if a prescription is written for b.i.d. dosing for a drug, the label of which says it can be given q.d. And that specifically I know has happened with losartan, so that although that shouldn't

prevent any doctor from doing what he thinks is right and patients taking what they have to take and all, nonetheless it would be useful to know what the effects of q.d. dosing are. And we'll get to the issue of whether it's useful to know what the relative effects of two drugs in q.d. dosing are, but I think it's important to recognize that this is a practical issue and this is useful information.

Go ahead, Eric.

DR. MICHELSON: This was a study done --

DR. BORER: Eric, excuse me just one second.

Tom?

DR. FLEMING: Before we leave this point -- this is such an important point -- I'd like to understand what Bob Temple's comments were just a moment ago. On page 14 in the FDA briefing document, we have presented to us data on losartan at 25 q.d. against b.i.d. at week 12, and differences were a drop of 5.8 versus a drop of 8, which is 2.2 millimeters of mercury. Bob, you had referred to these earlier as trivial differences. So, basically a 2.2 is a trivial difference?

DR. TEMPLE: I don't think they're trivial. I think they rarely -- I can't tell you whether in this case they did. They often don't reach statistical significance, and indeed, when we draw the dose-response curve for most of these things, the difference between the very highest

dose and the next dose often doesn't reach it either. We sort of look at the whole curve, and you do the best you can because you'd need 1,000 patients to distinguish between the very highest dose and the lowest dose, just as you just saw. So, we think it serves people better to write the description and the general idea of what the dose response looks like than to not say anything.

But if you ask how rigorous is that, first of all, it's usually based on data pooled across multiple studies which is of different durations, different populations. You could criticize it if you wanted to treat this rigorously. We're trying to give an impression, and in some ways that's the best you can do with realistic numbers.

Similarly, although this varies from one case to another depending on how well people look -- and that is very variable -- the b.i.d. versus o.d. comparisons are often treated somewhat qualitatively. It wouldn't surprise you that when the half-life of the drug is relatively short, we're more inclined to think maybe that's true that b.i.d. works better than once a day than when the half-life is 24 hours. So, I'm just saying there's a certain qualitative aspect to those aspects of it. That's not the fundamental efficacy data which we wouldn't treat qualitatively, but the descriptive aspects of dose response

are just inevitable when you're looking at multiple doses with relatively modest differences as you get to the higher doses or b.i.d. versus o.d.

DR. FLEMING: So, if have data that suggests a 2.2 millimeter difference, then you consider that irrelevant.

DR. TEMPLE: Absolutely. You'd say you might try b.i.d. if the patient doesn't give you an adequate trough response to o.d. If the half-life is 36 hours, we're less inclined to put that in because it's sort of implausible.

DR. BORER: Eric.

DR. MICHELSON: Dr. Armstrong, would you like to readdress that question just quickly?

DR. ARMSTRONG: Yes.

DR. MICHELSON: You saw the dose response for and can I address --

DR. BORER: Paul, did you have any other issues?

DR. ARMSTRONG: No.

DR. BORER: Let me just ask Tom as our reigning hypertension expert sitting at the table here, do you have any specific issues you want answered here?

DR. PICKERING: Thank you, yes. I'd like to hear more information about exactly how the peak and trough

blood pressures were measured. And related to that, you're inferring that because both showed a significant difference of a sustained effect over 24 hours, but I didn't hear whether you have any actual data using 24-hour recording to show the difference is sustained.

DR. PAPADEMETRIOU: Yes. The peak blood pressure was measured at 6 hours after dosing, and the patients followed all the usual procedures we follow in these studies. They were seated in a quiet room with a pressure cuff placed appropriately and the pressure was measured three times and it was averaged. Then it was again measured the next day prior to getting their pill of that day. That was the trough 24-hour pressure measurement.

DR. PICKERING: And any 24-hour readings?

DR. PAPADEMETRIOU: In this study there were no 24-hour readings, but there are some data from a previous study that compared losartan to candesartan that did 24-hour readings, and if you like those data, we can show them to you.

DR. PICKERING: Yes, please.

DR. PAPADEMETRIOU: Here is a study that was done in 106 patients that received candesartan and 100 patients that received losartan. The candesartan was 16 milligrams, losartan was 100 milligrams. And all these

patients had 24-hour readings. They had a baseline monitoring and then they had it at the end of the treatment period. In fact, the monitoring was for 36 hours. And you can see the average diastolic pressure for losartan, the change from the baseline here and the change of diastolic pressure with candesartan of the same time period.

We also have these data for the systolic blood pressure, and again in the same patient population, you can see the systolic blood pressure reduction with losartan and the systolic blood pressure reduction with candesartan. And you can see that pretty much the lowest values were obtained around this time.

Maybe it's important to note that these studies compared 16 milligrams of candesartan to 100 milligrams of losartan.

DR. LINDENFELD: Could I just ask a question about this slide? On page 10 of the briefing booklet, I was impressed by the blood pressure values at 48 hours and 2 weeks after withdrawal of your drugs. In fact, at least in the diastolic blood pressure, there was almost no difference. So, that's very different than this. In other words, it says here that after 2 weeks of withdrawal they were still low. Is that correct? 48 hours?

VOICE: Two days.

DR. LINDENFELD: Okay, two days, but even so at

48 hours after withdrawal, the diastolics were exactly the same with both drugs. That's very different data than this.

DR. PAPADEMETRIOU: For this study?

DR. LINDENFELD: Right, on page 10. Isn't that 48-hour withdrawal data from the CLAIM trials? Just help me understand this because I was impressed that at 48 hours a withdrawal of --

DR. PAPADEMETRIOU: We do have the 48-hour data from the CLAIM program that showed that difference is maintained.

DR. LINDENFELD: Right. That's 48 hours of withdrawal.

DR. PAPADEMETRIOU: Right, after the last dose, yes.

DR. LINDENFELD: That's my question because that's very different from this data that looks like at 36 hours the blood pressures come up again.

DR. NISSEN: I think I can help you clarify this. It's two different studies.

DR. LINDENFELD: No, I understand that. But I mean why in one study does the blood pressure start to climb again and in the other, when you withdraw the drug, it doesn't?

DR. PAPADEMETRIOU: These are the data we have

for 48 hours after the last dose in study 230, and you can see here that the difference is maintained. It's 2.8 and 4.6 at least 48 hours after the last dose.

DR. BORER: Those aren't quite as impressive as the trough at 48 hours before, which is the left-hand side of that slide I guess, but that's okay. What you showed us were data up to 36 hours after withdrawal. And I'm not suggesting you should have, but there is no information about the normal diurnal variation of blood pressure superimposed there. At 48 hours the numbers of both might have been a little bit lower than they were at 36.

Are you satisfied with what you got?

Blase and then Steve.

DR. CARABELLO: Obviously, the whole study rests upon the ability to measure blood pressure accurately. What do we know about site-to-site differences in the way in which blood pressures were measured? Was the same sort of device used? What was the actual mechanism of measuring the blood pressure?

DR. PAPADEMETRIOU: Well, the blood pressures were measured in a standardized way. All the centers were instructed to follow the same directions, to ask the patients to be seated in a quiet room for at least 5 minutes and relax without bright lights and any distractions.

Well, these are the instructions that were given to our centers of how to measure the blood pressure. The patients were seated for 5 minutes, a sphygmomanometer was used with a column and the appropriate cuff for the patients was used, and the right arm was used almost in all patients unless there was a reason not to. And the Korotkoff signs were read, Korotkoff I for systolic and Korotkoff V for diastolic. Their determination was based on three sequential readings at 2 minutes apart, and they had to have less than 5 millimeters of mercury difference. Qualifying blood pressure was a diastolic between 95 and 114 at week 3 or 4 or occasionally 4 or 5. There was a discrepancy of the placebo run-in period. So, these instructions were given to all the centers and they were followed.

DR. CARABELLO: So, these were all manual cuffs?

DR. PAPADEMETRIOU: Right.

DR. CARABELLO: Thank you.

DR. BORER: Steve.

DR. NISSEN: Yes. I had a couple of questions.

In all four of the studies that we heard about, the range of entry blood pressures was 95 to 114. And I'd be interested in knowing if in the development program there is any comparative data for patients outside of that

range. Many of us see patients with relatively mild hypertension, and of course, there are individuals with very severe hypertension. So, this speaks a little bit to labeling issues here. I understand why that range was chosen, but I'm interested in whether there's any data for people outside of that range.

DR. PAPADEMETRIOU: I haven't seen those data, but Eric may know.

DR. MICHELSON: Dr. Nissen, we did studies looking at people with more severe hypertension, and those studies were included in the original label. There's one study called 117. We have patients with and without diuretic. We have no studies done that are active comparator studies directly looking at people with severe hypertension.

DR. NISSEN: And mild hypertension? There is data or not?

DR. MICHELSON: I'm sorry?

DR. NISSEN: People that are, say, in the 85 to 95 range and that sort of thing.

DR. MICHELSON: No, we have no direct comparative data in that population directly. We have done studies in populations that include diabetics, for example, where the ranges are a little bit lower, but no direct data.

DR. PAPADEMETRIOU: There is an ongoing study, a trough study, utilizing patients with high normal pressures.

DR. NISSEN: I'm interested in that data, but it's not available.

DR. PAPADEMETRIOU: There is no data yet.

DR. NISSEN: All right.

And then my second question was related to the diabetes issue. Given the high body mass index of these patients, I would have guessed that many of them were diabetic, and I would be very interested. These are tough patients to treat, and a little bit of improvement in efficacy, as I think everybody in the room knows, in the diabetic patient is particularly important at reducing events. So, I'd love to see that data.

DR. PAPADEMETRIOU: The percent of diabetics included in the study was rather small. It was about 9 percent, but here we have 107 patients with diabetes, and compared to the rest of the group, they did have pretty much the same response in systolic and diastolic.

DR. NISSEN: And the point estimates are very similar.

DR. PAPADEMETRIOU: Yes, right.

DR. NISSEN: How could you manage to enroll patients with that body mass index and not have a third of

them diabetic?

DR. MICHELSON: These are patients who admitted to being diabetic by virtue of the medications that they were taking. So, you might think that in that pool of 50 percent of our patients -- 45 percent who had body mass indexes greater or equal to 30, one would suspect there are many hidden diabetics there.

DR. NISSEN: Or metabolic syndrome patients.

But this actually is helpful because it looks like the point estimates are about the same. Obviously, the confidence intervals are much bigger because it's a small subgroup.

DR. BORER: Are there any other questions of fact? JoAnn.

DR. LINDENFELD: Just two questions. You said at the beginning the study was planned to enter 735 patients and yet 230 and 231 both entered about 100 less than that. Can you tell me why that is?

DR. PAPADEMETRIOU: Right. These were comparative studies and investigators are more likely and more enthusiastic in entering patients in comparative studies because there's no long placebo treatment for any group of the patients. And the recruitment went very fast, so it was estimated that with 925 patients or so that were screened, that they would provide adequate numbers to

randomize 735. It turned out, however, that when the screened patients reached that number, the enrollment was closed. However, as they were progressing in the assessment for randomization, a greater number than expected did not qualify primarily for blood pressure, and it just turned out that the randomized patients were less. However, the number randomized gave enough power to provide a statistically significant result.

DR. LINDENFELD: These were concurrently run studies?

DR. PAPADEMETRIOU: Right, they were concurrently run.

DR. LINDENFELD: And another question. Were patients who entered these trials withdrawn from antihypertensive medications?

DR. PAPADEMETRIOU: Yes, about two-thirds of them were on medication. They were withdrawn from that.

DR. LINDENFELD: Can you give us some idea if the drugs that they were taking prior to randomization ended up to be the same in both groups? In other words, just by classification, ACE inhibitors, ARBs, beta blockers. Were the two groups equivalent in the drugs that were withdrawn?

DR. PAPADEMETRIOU: Right. I think we have that data available. Here, between the two groups,

candesartan and losartan, ACE inhibitors, about the same, 22 to 23; ARBs about 12-14 percent; diuretics, calcium blockers combination, and beta-blockers. Just about the same percentages.

DR. BORER: Bob?

DR. TEMPLE: I'm going to say something. You tell me whether you agree or not. Because there was no placebo here, the absolute falls from baseline are really unreliable. You don't know how much of those changes are just a part of the study. It's usually 3 to 5 millimeters of mercury in a typical trial. So, the absolute numbers are not reliable, but the differences are or could be.

DR. PAPADEMETRIOU: Right. I totally agree with that. We cannot say what was the absolute effect of either therapy.

DR. LORELL: One question that I wanted to address that's raised by your least squares analysis is the response in comparison of the black subset population.

DR. PAPADEMETRIOU: I'm sorry. I can't hear you.

DR. LORELL: In your least squares analysis, I'd like your comments regarding the comparative data in the black population subset.

DR. PAPADEMETRIOU: Yes. The black population was small, as you saw. The numbers were small, and the

data were not designed to assess statistical significance in these subgroups. We just showed them for the interest of everybody, but because of the many subpopulations and the issue of repeated measures and the small number of patients, statistics were not done in these patients.

But you can see the reductions in pressures in the subpopulations. We have them here, and we know that African Americans don't respond usually as well as the caucasian patients to ARBs or to ACE inhibitors, and this was true for these studies also. But they demonstrated a 6.4, 7.7, 8.2, and 6.6 reduction in diastolic pressure, and that is consistent with previous data that we have seen.

DR. LORELL: I think my question is a little bit of a different one. Today you're seeking labeling for a comparative analysis, so it's not addressing the overall issue of choice of an antihypertensive in a black patient. So, I guess my specific question is in the least squares analysis that you presented, it at least raises the possibility or the hypothesis that the comparative better efficacy claim might not apply to the black patient.

DR. PAPADEMETRIOU: Certainly that appears to be true from the data, but we can't say one way or the other because the population was underpowered to determine that. I think if we want the answer to this, we should design a prospective study in African Americans, which I

would support.

DR. BORER: Mike.

DR. ARTMAN: If we define control of hypertension as a sitting diastolic blood pressure of 90 or less -- I'm just trying to sort out. It's probably in here somewhere, but it's hard for me to figure out what percentage of patients were controlled. I think that's what a lot of clinicians are going to want to know.

DR. PAPADEMETRIOU: We do have that slide for both studies 230 and 231. You can see here the controlled patients with diastolic below 90. The number was a little higher for candesartan compared to losartan. It didn't reach statistical significance in this study, but here with a little bigger difference in the average pressures, the difference was statistically significant. So, there were about 9 percent greater patients controlled with candesartan in the second study.

DR. NISSEN: Michael, can I follow up on that and just ask is there data on systolic pressure? Many of us are much more interested since that's the metric that has the most relationship to outcome.

DR. PAPADEMETRIOU: The controlled patients by diastolic and systolic pressure are here. Again, the same trends were noted. The controlled were 36 versus 31, and this is true for most of the studies we do. We know

systolic pressure is more difficult to bring below 140, and it's easier for diastolic to bring below 90, and that's why the percentages are lower. But again, the trends are consistent.

DR. NISSEN: Actually the relevant one is the third pair of bars over there, which is the systolic pressure.

DR. PAPADEMETRIOU: Yes.

DR. NISSEN: So, it looks like it's 48 percent versus 46 percent.

DR. PAPADEMETRIOU: Right.

DR. BORER: Not to belabor the point -- and you may not have these data -- but the importance of systolic pressure seems to be age-related. So, I wonder if you looked, since you had an age range up to 80, at people over 55 for whom a systolic pressure really does seem to be the most predictive measure. You may not have this.

DR. PAPADEMETRIOU: There is a breakdown of the population below 65 and above 65.

DR. BORER: That would be fine.

DR. PAPADEMETRIOU: Here are the data for the patients over the age of 65, and the point estimates are pretty much the same.

DR. BORER: Okay, that's great.

I think Paul will have some questions about

drug-drug interactions, safety here, because we're not going to get into it in any other portion of your presentation.

But just before he does, can you just explain to me -- I'm sure this is some anomaly, but how did 100.5 and 100.3 percent of people in the study comply with the drug regimen? That was in the CANDLE study, not in 230 and 231. But just for our information.

DR. MICHELSON: We apologize for our implausible compliance numbers. Those are based on tablet counts, and so what's happened is for 2-week visits enough tablets are dispensed, for example, 20 days, and then someone comes back and tablet counts are done. So, it's conceivable that the tablet counts could be greater than 100 percent depending on what day they might come back.

Well, let me just give you something that's a little bit more relevant. If you ask me, for example, what percentage of patients took at least 90 percent of their tablets, as best we can tell by those tablet counts, I can tell you that in each of the studies for each of the treatments overall it might be about 93 percent of patients took at least 90 percent of the tablets they were supposed to have taken in any 2-week interval.

DR. BORER: It sounds pretty good.

Paul.

DR. ARMSTRONG: A few questions on safety. In the label that exists, there's some discussion of drug interactions that do not occur. Is there now information on, for example, spironolactone, amiodarone, other drugs that these patients would commonly be on which are not currently articulated in the label but for which you have new information that would be relevant to ACE inhibitors?

DR. PAPADEMETRIOU: I don't believe any of the patients entered in the trials were on these medications. I don't believe these data are available.

DR. ARMSTRONG: The second question. In table 12, page 44 of your briefing document, could you just reassure me? The dizziness appears twice as common in the candesartan versus the losartan group. Was that clinically meaningful? What are we to make of this? Was it related to blood pressure decline or other things?

DR. PAPADEMETRIOU: The dizziness was reported in a good number of patients, as you said, but it was not temporally related to any excessive lowering of blood pressure. And when patients complained of dizziness in the clinic and the pressure was measured, it wasn't found to be low. And it was kind of a sporadic reporting of dizziness. It was reported in the baseline run-in period. It was reported during the treatment period and afterwards. And it didn't seem to be related to any excessive blood

pressure lowering.

DR. ARMSTRONG: And the final question, on page 58, there's an interesting discussion about the difference in the two agents related to uric acid. Since many of these patients that presumably these drugs will be used in, of course, will have gout or a tendency towards gout and your label will speak to comparative superiority or efficacy relating to lowering of blood pressure, would you also be wishing to warn physicians about its use in patients who were susceptible to gout or had gout from the standpoint of the disadvantage of candesartan versus losartan?

DR. PAPADEMETRIOU: These are the data on uric acid here. Yes, it is true that losartan has slightly better uric acid than candesartan. In fact, candesartan had no effect one way or the other. But this is debatable what kind of clinical importance it has, and I think Dr. Kannel would be more appropriate to discuss his data from his large cohort in Framingham. As you know, this issue has been debated one way or the other, but at the current point, there is no certainty that it plays any significant role as a risk factor.

DR. ARMSTRONG: So, has no patient had an exacerbation of gout or the development of de novo gout treated with candesartan?

DR. PAPADEMETRIOU: No patient had exacerbation of gout or a new onset of gout.

DR. ARMSTRONG: Thank you.

DR. BORER: If there are no other substantive questions from the committee, maybe we can move on to Dr. Kannel.

Oh, I'm sorry. Tom.

DR. FLEMING: Just a very quick additional because JoAnn had asked a question that I was interested in too. I'm troubled a bit by the substantial discrepancy between your intention of 735 patients. For example, in the 230 trial where you had 611, at what point did you discover that you were well short of your target relative to the unblinding?

DR. PAPADEMETRIOU: That was certainly after the enrollment was closed and after the baseline placebo run-in period was completed. And the sponsor decided that it was too late to go back and reopen the screening phase.

DR. FLEMING: And at that point, of course, all outcome data were still blinded.

DR. PAPADEMETRIOU: Yes.

DR. BORER: Okay.

DR. PAPADEMETRIOU: Dr. Kannel.

DR. KANNEL: Good morning. I'm pleased to have the opportunity to review with you some of the data that

are available to us on the epidemiological and clinical significance of incremental changes in blood pressure based on some of our data from Framingham and based on large data sets from epidemiological studies that are prospective and also on clinical trial data.

I think we would all agree that hypertension is a major treatable risk factor for cardiovascular disease. It is a powerful independent risk factor for coronary disease, for stroke, for peripheral artery disease, and heart failure. I hope to convince you that the relationship is continuous and graded, that there are benefits of blood pressure reduction with pharmacological treatment that are also incremental and continuous.

Framingham data on coronary disease and also on cardiovascular disease in general indicate that hypertension is a major risk factor in the occurrence of these atherosclerotic cardiovascular events, and it certainly compares with elevated cholesterol and smoking probably in terms of the absolute risk having a greater impact, and only for diabetes in women does it seem to not be dominant. This is true also for the risk ratios comparing those with and without the abnormality. Risk ratios for hypertension are more impressive than for the other outcomes.

If one looks at the risk for a cardiovascular

event by, in this case, diastolic blood pressure, you note, of course, that for the individual, as the blood pressure increases, so does the risk of having a cardiovascular event, and this is incremental throughout most of the range for diastolic pressure. It's also interesting to note that if one looks at the occurrence of disease in the population, as indicated by the bars, at specified intervals of diastolic blood pressure, that most of the events are coming from those with high normal or stage I hypertension.

Looking at the same relationship for systolic blood pressure, over 38 years of follow-up in the Framingham study for subjects aged 35 to 64, we see an even greater influence of the systolic blood pressure than the diastolic, again an incremental increase in risk from the very lowest to the very highest systolic blood pressures. This indicates that certainly for the individual the risk increases, the higher the blood pressure. But once again, we see that for the population most of the events are coming from people who have high normal or grade I hypertension.

We have an even more impressive data set, which includes the Framingham study, from MacMahon published in Lancet in which they looked at the data from seven prospective studies involved with stroke and nine

prospective observational studies with coronary disease from which there evolved 843 stroke events and almost 5,000 coronary events. In all, we're looking at databases of more than 400,000 people. This gives a very, I think, compelling indication that there is a graded influence of blood pressure on the risk of events, going down well into what we might consider the normal range, for both stroke and for coronary heart disease. The confidence intervals are very tight, so these estimates are, I think, very secure from a statistical standpoint.

Now, based on these, MacMahon has estimated what sort of reduction in risk one could see with specified reductions in diastolic blood pressure between the range of 5 and 10 millimeters of mercury, and he shows that the more the blood pressure is reduced, the greater the benefit, that this is true both for coronary disease and for stroke, and the reductions are substantial. And there is an incremental benefit the more the blood pressure is reduced both for stroke and coronary disease, more impressively for stroke than for coronary heart disease.

Now, these observational studies show rather similar risk reductions with changes in blood pressure achieved. The estimates from the observational studies, when applied to the drug treatment trials for stroke, indicate very, very similar outcomes. We see almost

identical results. For coronary disease, the observational studies seem to overestimate the benefit a bit, but it's important to recognize that both databases show the more the blood pressure is reduced, the greater the benefit and that there is a distinct incremental benefit to further reduction in blood pressure.

Another way to evaluate the importance or advantage of additional blood pressure reduction is to look at the number needed to treat to prevent an event, and the event that's most feared in hypertensive patients is stroke. Here we've indicated the Framingham average risk over 10 years for having a stroke for average-risk and for high-risk individuals. The high-risk individual is the one who is a smoker, has a blood pressure of 100 millimeters of mercury, already has some indication of cardiovascular disease, a reduced HDL, high cholesterol. I think several points are noteworthy.

First is that looking within this category, let's say, of a 5 to 6 millimeter of mercury reduction in diastolic blood pressure, one sees that the number needed to treat to prevent an event is about 28. On the other hand, if you're applying this to high-risk individuals, the number needed to treat is substantially lower. But if you look and see if you can reduce the blood pressure by an additional 2 or 2.5 millimeters of mercury, in the average

patient you get a substantial reduction in the number needed to treat, and also in the high-risk individual, you see a substantial reduction in the number needed to treat to prevent an event.

Looking at this for systolic blood pressure, I think the SHEP and Syst-Eur trials are the two that give us a pretty good idea for isolated systolic hypertension as to the benefit of lowering systolic blood pressure within these ranges with achievable blood pressure reductions as indicated here. We see a very impressive reduction in stroke in both trials, total cardiac events, and total CVD, combining both.

Now, given this demonstration of the benefits of antihypertensive treatment, it's rather disappointing to see that we still have only 68 percent of hypertensive patients aware that they have the thing, that only 54 percent are treated, and that only 27 percent are controlled.

Also somewhat discouraging are these surveys of general practice and how physician practices look in the treatment of hypertension, one by Coppola in the Journal of Human Hypertension, one by Berlowitz, et al. in the New England Journal of Medicine very recently. And we find that hypertension, particularly isolated systolic hypertension, is seldom treated to the recommended goal,

that if you look at patients who have hypertension who come back to see their physician on a return visit, that they receive no increase in medication 75 percent of the time despite their having a continued blood pressure elevation. We also see that the drugs are rarely up-titrated, that there's a reluctance to include additional drugs. Therefore, we would conclude that therefore more effective monotherapy drugs could facilitate attaining recommended treatment goals.

So, the conclusion seems to me justified to reflect on the importance of incremental blood pressure reduction, that hypertension is in fact a major treatable risk factor for cardiovascular disease, including coronary disease, stroke, peripheral artery disease, and heart failure; that incremental blood pressure reduction is meaningful from a public health standpoint and also in clinical practice; that the benefits of blood pressure reduction with pharmacological treatment are incremental and continuous; and that there is a compelling need for clinicians to use the more effective blood pressure reducing drugs to achieve recommended goals in individual patients.

Thank you.

DR. BORER: Thank you very much, Dr. Kannel. These are, of course, very useful data.

Are there any specific substantive questions for Dr. Kannel? Steve.

DR. NISSEN: I'm going to try to articulate this and I hope I'm able to do it. In trials where blood pressure is lowered, there are two issues. One is the magnitude of blood pressure reduction, and the other is the class of agent used to lower blood pressure. So, I have two questions, and maybe we don't know the answer to any of this, but I'd be interested in your perspective.

One is, if you have a drug in the same class -- so, intraclass differences -- and one drug in that class lowers blood pressure by more than another, what might we anticipate about lowering events versus two drugs in two different classes? In other words, if you lower blood pressure by 12 millimeters with a diuretic and by 10 millimeters with an ACE inhibitor, you expect that the diuretic will lower events by more than the ACE inhibitor. Now, that's somewhat of a rhetorical question, but I'm interested in your perspective on the issue of intraclass versus interclass differences in event rates when looking at blood pressure reductions.

DR. KANNEL: The first point is that we have no data which have compared rigorously individualized therapy for hypertension versus across-the-board therapy using a single agent. So, we really don't know. I don't think

that trial is even ever likely to be done.

Now, there is some indication from various studies that there may be unique effects of some antihypertensive agents aside from their blood pressure lowering effect. That's not to say, however, that given this unique effect within that class of drugs, the more you lower the blood pressure, the better off you are. And I think the indications are that that's the case.

Now, if one looks at trials, let's say, such as those trying to reverse left ventricular hypertrophy with different agents, you find that no matter which agent you use, if you lower the pressure enough and keep it low, you will reverse LVH. On the other hand, some agents seem to do it quicker and to a greater degree than others. For example, I think there's some evidence that ACE inhibitors will get you more reversal faster. So, I think it's clear that there's an impact of the class of drugs as well as the amount you change the blood pressure.

DR. BORER: Bob.

DR. TEMPLE: Well, there have been attempts to look at that. There are these massive meta-analyses, and they compete with each other based on the bias of the people going in.

(Laughter.)

DR. TEMPLE: But my dominant reaction to them

is that the results are more alike than different. You can argue about whether one does stroke a little better than the other or one does this a little better, but what impresses me most is how little difference there is even if there might be some small difference.

And these are massive numbers of patients. You know, you get over 25,000 in some of these things, and of course, we also have ALLHAT, which is to some extent attempting to answer the same question. They found one difference with doxazosin, but the study is still going, as far as we know.

DR. NISSEN: I guess I was really maybe trying to get the point on the floor that we may need to view intraclass differences and interclass differences differently in terms of the potential here.

DR. TEMPLE: Yes. I would say our thinking on that is that across classes there are many things to think about. I mean, what a diuretic does and what an ACE inhibitor does is different in a lot of ways, and they're not purely interchangeable although someone might say, oh, well, I think this one should be used first or that one should be used first for various reasons. But within a class, you generally think other things are mostly equal, so it might be that a difference in effectiveness is a more pure determination.

DR. NISSEN: That was really the point I was trying to drive at. For example, diuretics increase insulin resistance and that may yield other results that would be less desirable. So, I have a lot of trouble interpreting small differences in blood pressure between drugs in two different classes. I have less trouble in interpreting them within a class.

DR. BORER: The question I was going to ask you, which you answered several times, but I'll restate just to hear a yes or a no or anything else you want to say. My inference in reviewing the epidemiological data before this meeting specifically for the meeting was that the issue of control that was raised in several questions is based on a consensus construct about the importance of reducing events at least to where an inflection point, an event rate, occurs which is somewhere around 90 to 95 diastolic and somewhere around 140 systolic, but that the risk associated with a blood pressure continues to be lower the lower you go even below that level of control, which may be important in interpreting the results of these trials we've seen. I assume that's correct.

DR. KANNEL: I think the overwhelming evidence, at least as I see it, is that there's a continuous, graded influence that goes down into what's considered the normal value. If you follow the recommendations for hypertension

over decades, you can see in the old days they said 100 plus your age is normal, and the pressures that were considered worthy of treatment were really spanking high blood pressures. And some felt that to lower blood pressure was a foolish thing to do, particularly in the elderly. We're now down at the point where we're considering the fact that perhaps even real modest elevations of blood pressure carry a substantial risk.

Now, over the years in Framingham, we've been tracking the level of blood pressure at which events are occurring, and every decade the average level at which events are occurring goes down and they are now down to levels which are quite modest. So, I think we're going to be focusing increasingly on treatment of real modest levels of pressure. That's where the incremental benefit of lowering blood pressure becomes very important because I indicated that most of the events are coming from these modest blood pressure elevations.

Now, to control really severe hypertension, you need more than monotherapy. You have to use two or three drugs. But if you get down to these levels, to push them down to some goal that JNC VI or VII is going to recommend, you can maybe achieve it with monotherapy if you have a stronger drug.

DR. BORER: Thank you very much.

If there are no specific questions -- oh, I'm sorry. Paul.

DR. ARMSTRONG: Dr. Kannel, there's a lot of discussion in the physiology literature, as you know, about pulse pressure and about the number of times the blood pressure is elevated with an individual's stroke volume per minute. Do you have data? Are there data? There obviously are data out there. What are your views about targets apart from the conventional ones?

DR. KANNEL: Well, I think the field is in evolution, and I think we're going to see more recommendations that focus on systolic pressure and pulse pressure and arterial compliance. Some of the data your quoting, which actually come from Framingham and were done by Stan Franklin, would seem to indicate that in an earlier stage of life in the 30s, one sees a dominant effect perhaps of diastolic pressure. Then it moves on to systolic and finally to pulse pressure as you get older and older. And as one looks at control, you saw that there was only about 50 percent control to the recommended levels. But if you look at that in some detail, you find that most of the lapses or inability to achieve control is occurring in failure to control systolic pressure. We found this in Framingham. Others have found it in NHANES that this applies to African Americans, to Hispanics, as well as to

caucasians and even diabetics. So, the chief problem seems nowadays to be in failure to pay enough attention to systolic pressure and to controlling the systolic component of the blood pressure.

DR. BORER: Thank you very much again.

Dr. Lancaster, do you want to sum up?

DR. KANNEL: Yes, I would like to ask Cindy Lancaster to come up.

MS. LANCASTER: I'm coming. I'm coming.

(Laughter.)

MS. LANCASTER: Thank you, Dr. Kannel.

As previously mentioned, AstraZeneca met with representatives from the Division of Cardio-Renal Drug Products, the Office of Drug Evaluation I, and DDMAC to obtain guidance about how to develop a program to support comparator labeling. Based on this guidance and labeling precedents of other antihypertensive products, AstraZeneca developed this comparator text to supplement the information already described in the approved labeling for Atacand within the context of its approved indication, which is for the treatment of hypertension. This is important information for health care providers, and therefore AstraZeneca has proposed its inclusion in the labeling.

In summary, the proposed labeling describes the

statistically significant results from two trials comparing the blood pressure lowering effects of candesartan cilexetil and losartan in hypertensive patients. The labeling is specific to effects on blood pressure reduction.

AstraZeneca will continue to work with the division to finalize labeling, and we thank you very much for this opportunity this morning to present the information to you today.

DR. BORER: Thank you very much.

Before you go away or we take a break or anything, I'd like to ask you a question to which there really, I think, is no absolute answer and I think maybe we've gotten the best answer from Dr. Kannel's presentation. But we're talking here about amending a label with regard to lowering blood pressure and the relative efficacy of a drug in lowering blood pressure compared with another drug.

One might question the strength of data to support the clinical implications of changing that surrogate. Now, I'm not suggesting this is bad, good, or indifferent. I just want to understand what your thinking is in summary about the clinical implications of changing the surrogate that we measure in this particular circumstance.

This is an issue that was raised by the FDA medical reviewer in his review. I don't know that I would completely agree with the statements that were made there, but it doesn't matter. I'd just like to have a summary statement about what you think about what this blood pressure lowering means clinically since all we're measuring is blood pressure lowering.

MS. LANCASTER: I'd like to invite Dr. Papademetriou to come up and comment on clinical significance.

DR. PAPADEMETRIOU: We believe when we treat patients with hypertension, that the best blood pressure reduction we get, the better the patient will be in the long run. The lower the blood pressure, the better it is for the patient in preventing complications.

The physicians I think will benefit by having all the data available to them when they are trying to make a decision what will benefit their patients most and what is more likely to bring them to target and get their pressure to the level they want. I think this is the implication I see.

DR. BORER: And I certainly couldn't disagree with that. What I was really sort of driving at here, though, was that this was not an outcome trial, and you can't be held to a standard that isn't the standard we use.

But if you look at the events here, there was one myocardial infarction in a patient who was on candesartan and none in the losartan group. Does that mean anything at all? Are we using the right surrogate?

DR. PAPADEMETRIOU: Well, this is a fairly large study with 1,100 patients and these are patients that have a lot of other risk factors. They have hypercholesterolemia, previous history of coronary disease, vascular disease, and events happen unfortunately, even when we treat those patients adequately. I think these events are incidental and they are not drug-related and they're not attributed to an excessive lowering of blood pressure for one thing. We have many, many data sets from many, many studies indicating that lowering the blood pressure to lower levels is beneficial.

DR. BORER: Tom.

DR. FLEMING: Well, since you've gotten into this, maybe we'll talk more about this after the break. I've always been troubled by use of surrogate endpoints, and there is more of an argument in a blood pressure setting for having more reliance on this as a marker. I view these as very small studies.

Clearly there's a lot that's not known about what the actual true relative efficacy is. The differences in blood pressure are not efficacy differences. They're

differences in markers. And the data that we've seen certainly indicates that there is a correlation between reduction in blood pressure and reduction in stroke and other clinically important events.

Many things are uncertain to me. One is we're looking at this at 8 weeks. What is the necessary time frame and what's the magnitude that we would have to see in order to know that we have a certain clinical benefit?

Steve got at a very important issue before and that was different interventions can have many mechanisms by which they achieve clinical benefit. Patients should choose those interventions that yield the overall global optimal benefit-to-risk profile. Blood pressure is one mechanism by which adverse events occur, and there is certainly evidence that an agent that has a lower blood pressure, if it's adequately lower for an adequate duration of time, will in fact favorably impact one of the mechanisms by which adverse events occur, but we don't know about the other mechanisms. This was on a clinical endpoint study.

Safety issues are also relevant here, and I'm perplexed about knowing how much safety data we would need to have. The questions that are going to be posed here indicate up front that we really need to understand that if we achieve "superiority" in benefit that it's not coming at

the expense of safety. These studies are not really powered to be able to look at relative serious safety events. There are more safety issues in the candesartan group, I think twice as many SAEs and one-and-a-half to two times as many people withdrew for AEs.

So, I'm a bit perplexed about what is an adequate amount of information in understanding benefit to risk because presumably, if one is going to label an intervention as being superior, that's conveying a sense that it's better to use that agent, which ought to mean more than just through one of the intended mechanisms.

Another issue that we'll get into -- and maybe I shouldn't even raise it because it's, in a sense, a separate issue is the issue of what is the right dose and schedule to assess. I'm a bit troubled, when we need two adequate and well-controlled studies, to be doing two studies that are both very small and essentially identical. It's really one study. Would it have made sense that we would have had two studies and a second study would have looked at a different schedule, specifically b.i.d. instead of q.d.? But that's really a separate second issue from the first.

DR. BORER: Okay. If there are no other questions or discussion at this point, we will have other discussion in the context of the FDA questions.

It's now 9:55. We'll take exactly a 14-and-a-half minute break and come back here at 10:09 and 30 seconds.

(Recess.)

DR. BORER: Okay. Let's get together again, if we can, and complete this morning's session.

We have a series of questions from the FDA, and we'll orient our discussion around the questions. Now, Doug Throckmorton, if you're here yet, we need to know which questions you want a specific vote and reason from each member about.

The Cardio-Renal Advisory Committee is asked to provide an opinion on the relative antihypertensive efficacy of a regimen containing candesartan and a regimen containing losartan. Specific guidance is sought on how to describe any relevant differences in labeling and on the adequacy of the advice that we've given sponsors to guide future development programs. There is little published experience or relevant guidance, but this issue is briefly addressed in ICH guidance E-10. And for the record, it should be noted that everybody on the committee received a copy of that quite a while ago to read and review for this meeting.

In the past the agency has told sponsors that demonstrating superiority to another antihypertensive

medication on blood pressure lowering, when both were appropriately dosed, was a relevant clinical benefit and that such a claim required the following data:

First, evaluation of the antihypertensive effects of the respective drugs at the highest approved doses. If the comparison was not done with the approved product, bioequivalence of the study formulation and the approved product must be demonstrated. Our recommendation has been that this evaluation should include at least two forced-titration trials to adequately assess the drug's relative antihypertensive effects. We have also said that unless a placebo group is included in the trials, no information about absolute antihypertensive efficacy can be inferred, only comparative antihypertensive effect.

Two, data comparing the safety of the two agents, providing evidence that the superior agent is not inferior with respect to safety.

The present sponsor has provided data from three randomized trials, including two forced-titration trials. These were conducted comparing candesartan force-titrated to a dose of 32 milligrams per day and losartan force-titrated to a dose of 100 milligrams per day. The agency and the sponsor agree on the numerical results of the efficacy analyses for the three trials. At the end of 8 weeks, candesartan 32 milligrams reduced blood pressure

by about 3 and 2 millimeters of mercury systolic and diastolic more at trough than did losartan 100 milligrams, when both were given once per day.

So, we have our questions.

Which of the following are necessary or sufficient to establish a claim of relative superiority for an antihypertensive?

We'll have our committee reviewer, Paul Armstrong, provide an answer and then have anybody else comment or disagree if they want to. I'd like particularly to have comments on each of the questions from Tom Pickering, our guest committee member, and of course, from Tom Fleming, the committee statistician. Paul, go ahead. Number 1.

DR. ARMSTRONG: So, in response to question 1 -- I guess there are six subquestions there -- I would say yes to 1.1, 1.2, 1.3, and 1.4. I would say no, but desirable to 1.5, and I would raise the issues in 1.6 around pulse pressure and, of course, issues related to target organ that we have not discussed. That's how I'd deal with those.

DR. BORER: Tom, do you have any thoughts about this?

DR. PICKERING: I would agree that you need both diastolic and systolic significant differences not

only at trough but throughout the 24-hour period. I'm sort of somewhat surprised that the original discussion didn't include a request for 24-hour data on this, but I can't fault the sponsor for that. The mean pressure obviously would be redundant if both systolic and diastolic are reduced.

In terms of reduction of pulse pressure, my own view is that I think it would be premature to require that since I think it's difficult to show that individual drugs have significantly different effects on pulse pressure. And also, we really don't know in therapeutic terms what the implications are. So, I think for the present, it would be appropriate to stick to systolic and diastolic pressure.

DR. BORER: What about the issue of other measures of effectiveness, blood pressure being a surrogate? Do we need to have other measures of effectiveness besides blood pressure alone?

DR. PICKERING: Well, I think if the claim is merely one of superior reduction of blood pressure, then that's sufficient.

DR. BORER: Are there any comments from committee members that would differ? I'm sorry. Bob, you had a concern?

DR. TEMPLE: Actually I just wanted to ask Dr.

Pickering a question. There are two possible reasons that one member of a class could perform better than another. One could be that the absolute effect is different. The other could be is that one is more truly a once-a-day drug than the other. In that case, you might see similar effects at peak but different effects later because one of them is sort of forced into a once-a-day therapy when it really would be better twice a day. Would that not be okay? Wouldn't it be okay if it came out that way too? Not that that's a problem in this case, but it could be some other time.

DR. PICKERING: I think we really don't know. There is some data that when you're looking at regression of target organ damage, the average 24-hour blood pressure is the best predictor of the regression of increased left ventricular mass. Other than that, I don't think really one can say in terms of interpreting the blood pressure changes in either outcome or changes in target organ damage.

DR. TEMPLE: So, maybe if it weren't different at both peak, and trough, it would need to be buttressed with some 24-hour data showing an overall difference.

DR. PICKERING: Right.

DR. BORER: Steve.

DR. NISSEN: I think this is actually a really

important question. I want to say that I think we need to shift our thinking here. We were recently fooled into believing in a trial like HOPE that there was an independent-of-blood-pressure effect by the drug ramipril because we didn't really understand what actually happened. I think that we have to avoid that kind of confusion. It turns out that it was only a 3 millimeter difference in blood pressure reported, but it turns out, unbeknownst to any of us, it was a trough pressure measured long after the drug was administered, and when an ambulatory blood pressure study was done, the average 24-hour difference was 10 millimeters of mercury which actually more than explained the event reduction.

So, I guess what I'm trying to emphasize is what Tom said. To characterize blood pressure, we need to know much more than just trough pressure. We'd like to know really kind of what the area under the curve is. I think that in future development programs -- not this one, but in future ones -- we really probably want to see the peak and trough numbers but a substudy at least with some ambulatory blood pressure data to help us understand so we don't make the mistake that we made with the HOPE trial in actually taking a single trough reading and expecting that that was reflective of what the 24-hour blood pressure effect was.

DR. BORER: I'd like some comment from Tom and from Doug and Bob. But my understanding is that to this time there are no data that relate any parameter measured on a 24-hour ambulatory blood pressure and mortality and cardiovascular events or cardiovascular events. That doesn't mean it's not important to know, but what I'm suggesting is that this is an area where a great deal more information is needed so we know what to measure, but it's maybe hard to suggest that we should change the surrogate now.

Bob.

DR. TEMPLE: Well, the trouble is most of the drugs that have been studied for outcomes either have very long effects like diuretics, so peak and trough aren't that different, you know, reserpine and things like that. And almost all of these have effects on both peak and trough, and if you do that, it's hard to imagine that the overall isn't also affected because you wouldn't expect square wave changes or something. So, it's very hard to tease those things out. Therefore, no one has yet.

It may be with ever-huger studies, people could look at something that has a big early effect and a small late effect and see if there's any difference. But I'm not aware of anything like that either.

It would also help us to see where that HOPE

data are because 10 millimeters of mercury is bigger than the effect of those drugs that we've ever seen in hypertensives. So, that's a surprising result.

DR. NISSEN: It was driven largely by the fact that the nighttime difference was 17 millimeters of mercury. So, it turned out there was a very big early effect that tailed off very quickly. And until the ambulatory blood pressure data were published a few months ago, everybody was citing the 3 millimeter difference and saying it couldn't have been blood pressure, and now I think we realize that that was wrong. I think that kind of mistake is going to get made in the future if we're not careful about understanding the full 24-hour effect of an antihypertensive drug.

DR. TEMPLE: For what it's worth, essentially all antihypertensives now have ABPM data.

DR. BORER: Tom, do you have any other comment about that?

DR. PICKERING: No, but I would agree that while the new drug applications do, many of the large outcome studies have not included substudies. I mean, a particular example was the CONVINCE study where they were interested in different chronotherapy where it would have been very helpful to have 24-hour data. And HOPE is a classic example.

DR. THROCKMORTON: Steve, I want to press just a little bit. The question here sort of was layered. One part of it was what advice should we give sponsors as far as adequate evidence, and to date we've relied on trough data for the reasons that Bob pointed out. Obviously, we have those data as far as outcome. So, trough is where we've focused our energies.

What I'm hearing, though, is that there might be a couple of reasons why you might like other data. One, you might imagine that the drugs have different pharmacologic properties so that there's a big peak that wanes in one of them that maybe doesn't wane in the other. I don't know. Hard to imagine. But maybe you'd want to have that information.

Alternatively, you might imagine that you believe that those other measurements might, in fact, be a better way to look at benefit.

Can you help me sort of which way actually other people on the committee too are sort of thinking about that?

DR. NISSEN: What I was thinking I guess is this, that obviously you have to have a primary efficacy endpoint. I think the trough pressure is, in fact, the right one to have. But when we review an application like this, to me the presence of data showing differential

effects at peak as well as trough, on systolic as well diastolic help me define the effect as a robust one. Again, without necessarily proving to you that that kind of robustness will make it more likely to have a difference in events, which I know Tom is concerned about, it sure makes me a lot more comfortable if I have such data available as secondary efficacy parameters.

And of those data, the most, I think, robust is to see those 24-hour curves. I thought the 24-hour curves we saw on ambulatory blood pressure where the candesartan curve was always beneath the losartan curve makes me feel a little bit better about whether the effect is real.

Having said that, I think we might want to think about asking that the primary efficacy parameter shift from diastolic pressure at trough to systolic pressure at trough as we have new data that now suggests that it's a better predictor. So, that would be one shift I would suggest.

DR. TEMPLE: Yes, I should tell you we've been talking among ourselves about that. In fact, you should have an effect on both. It's not too much to ask. It's not that hard to show. They always do, by the way.

DR. BORER: Paul.

DR. ARMSTRONG: Well, having put the target organ issue out, let me come back, Mr. Chairman, and ask,

just to be the devil's advocate, whether the measurement of blood pressure has anything to do with the disease called hypertension and the consequences of stroke and myocardial infarction that Dr. Kannel and others have pointed out. It seems to me when we look at interclass differences, this issue sharpens.

So, I for one, as a doctor treating a patient, would like to be reassured that if the blood pressure is lowered, that there might be surrogates between the blood pressure measurement at one end and the stroke at the other that might reliably guide me as to the likelihood ratio of impacting long term on some of those phenomenon that I'd like to change.

So, what might be alternatives? Renal function or microalbuminuria as we've discussed around this table before. Left ventricular hypertrophy, quantitative retinopathy. There are a variety of measures that are intermediate that reflect the health of the target organ with this disease that I think should be debated and discussed.

DR. BORER: Let me try and sum up, if I can, because this is not one of the questions you wanted a vote on.

DR. TEMPLE: But if we had an extra 4 or 5 days, we --

(Laughter.)

DR. BORER: I think what the general sense of the comments is is that 1.1 through 1.4 are essential. One might want to get there by using 1.5, but I suppose there are other ways you could do it. And it would be nice if there were some information suggesting that the pathophysiology of the processes that are putatively caused by hypertension are beneficially affected, but I think we're going to have a hard time without a workshop to come up with a guidance about how you would do that. Of course, nobody else has yet either.

So, let's go on to number 2. The sponsor compared once-daily dosing for both products, although both products are labeled for once- or twice-daily dosing. Is a once-daily comparison a legitimate basis for a superiority claim? Paul?

DR. ARMSTRONG: I would say yes, and I would add but the caveat is that it, of course, does not extend to b.i.d. dosing if a product has been marketed and suggested that it might be more efficacious if one moved from once to twice a day. But on the basis of the data we've seen and the way it's usually prescribed, the answer is yes.

DR. BORER: I think the issue was not so much for this drug, which we're going to get to in a later

question, but in general. I assume your comment is generalizable.

Does anybody on the committee have a different opinion about that? Tom?

DR. FLEMING: Well, I think this gets to this ICH E-10 guideline here indicating that it may be necessary to look at different doses of the control either through separate studies or through multi arms in the same trial.

If one conditions and says that in clinical practice, there's a strong preference for q.d. dosing and conditions this conclusion based on the assumption that we're restricting to q.d. dosing, then this is a legitimate comparison.

But if in fact there's evidence to suggest the control arm could, in fact, yield better efficacy with b.i.d. dosing than q.d. dosing, then I think one has to be very careful that one doesn't infer from your statements that, in fact, you have superiority relative to what the optimal schedule for the comparator regimen would be.

I think there's limited data in really understanding the efficacy of b.i.d. versus q.d. losartan. I had referred earlier to what was in the briefing document from the FDA on page 14. The magnitude of differences at 25 for b.i.d. and q.d. were at least as large as what we're focusing on as the difference between

candesartan and losartan.

So, my sense is if one were trying to infer from these data a relative efficacy against an optimal schedule, I think there are a lot of uncertainties about that. But if one says clinical practice is really interested in q.d. dosing, so we're going to condition on only that as a restriction, then these data are adequate.

DR. BORER: Steve.

DR. NISSEN: This one is potentially pretty treacherous. Imagine a drug for a moment that has a relatively short half-life but is very efficacious that, when given b.i.d., produces substantially better blood pressure reductions. And now imagine that such a drug is compared to another drug which is overall, when given once a day, actually less efficacious. You don't want to give a claim to a drug that's long-acting compared to a drug that's short-acting without giving the shorter-acting drug in a more fair way, which is b.i.d.

Now, clinicians may decide that the once-a-day drug, even though it's less effective at lowering blood pressure, is preferable on compliance basis, and that's fine.

But in terms of sticking by the rules, we were helped here by the fact that the peak-to-trough ratios for these two compounds are both in the .8 to .9 range. So,

it's kind of a fair comparison, but I could imagine another comparison where it wouldn't have been fair to use the primary efficacy parameter of trough pressure and compare once a day to twice a day. So, we ought to be careful here how we generalize this.

DR. BORER: Beverly.

DR. LORELL: Yes. I agree very strongly with that point. I think for the specific comparison that we're being asked to address today, for the reasons that Steve mentioned, the once-a-day comparison is very legitimate. But I too would have concern if this were used as a generic recommendation for potential present or future comparisons.

DR. BORER: Bob.

DR. TEMPLE: Let me try a distinction and see if this is what you have in mind. If one drug were labeled for b.i.d. use because that's the only way it works, and then someone said, okay, I'm going to compare my drug once a day because I'm a once-a-day drug with your drug once a day to show that it really doesn't work very well that way, we would probably have a lot of trouble with that because that's really sort of irrelevant. I think that's what you're saying.

DR. LORELL: Yes.

DR. NISSEN: I guess I'm saying a little more than that. Let me see if I can articulate it.

Some drugs which are labeled for once or twice a day that can be given either way have peak-to-trough ratios which are bigger, and so yes, it's true the drugs could both be given once a day, but where one drug perhaps is a bit more optimal when given twice a day, and so you're not clearly comparing a drug given in a way that's not in the label and saying you're superior to it. That's off the table.

But what about a drug that has a peak-to-trough ratio of .5 and comparing that to a drug that has a peak-to-trough ratio of .9, both of which in their label are allowed to be given once a day? I don't know that that's a fair comparison.

DR. TEMPLE: The reason we started asking a long time ago for peak-to-trough ratios -- I'll tell you a little bit of history, which you probably don't really care about. But we got a proposal to use hydralazine in a once-a-day treatment many, many years ago. And they measured only peak. Well, it worked very well at peak. But we said, does it still work when you look at 24 hours, and we found no. That was a revelation to us. We had never thought about that before, or much of anything else actually.

(Laughter.)

DR. TEMPLE: So, ever after that, we began

asking are you just taking a short-acting drug and giving a lot, maybe getting extra symptoms at peak just so you'll have a little bit of effect later and trying to get by. So, we don't like that. But as you pointed out, some drugs do lose some of their effect by 24 hours.

Now, one thought we've had is if that's what you're doing, if you're sort of stretching a short-acting drug and aren't going to the trouble to make a controlled-release product or something like that, maybe someone should be able to beat up on you by showing that you don't really work very well once a day. Now, that's not what this case is. These drugs do work once a day. But we hadn't necessarily thought that that was an unfair thing to do if they were both labeled for that. Now, if they're not labeled, as you said, off the table, but if they are, maybe that's not such a bad thing. I don't know. A good thing to discuss.

DR. BORER: This isn't one of those questions you require a vote about, but I'm going to provide one final comment, if I may. I think the answer to this is absolutely yes, it is legitimate to use the once-daily comparison as the basis for a superiority claim when both drugs are labeled for once-a-day use. That information is useful to the clinician who's going to use the drug that way. It doesn't preclude using either or both drugs

b.i.d., if one chooses to do that, because on the basis of observations made in an individual, one gets greater efficacy with the product using it in a different way.

But if the drugs are labeled for once-a-day use, which we know means they can't have a peak-to-trough ratio greater than a certain value -- I think it's .5 so that safety doesn't become an issue -- I think it's not only legitimate but useful to know what the relative efficacy of the drugs are when used in that way. So, I think it's legitimate.

Let's go on to number 3. Which of the following are necessary or sufficient to establish a claim of relative superiority for a once-daily antihypertensive? Paul?

DR. ARMSTRONG: So, 3.1, beating the comparator's highest approved once-daily dose? Yes.

Beating the comparator's most effective approved regimen? I would say no.

Beating the comparator when it is dosed to maximum, perhaps outside the approved dose range? I would say no.

Beating the comparator when used with other approved agents, such as diuretics and beta-blockers? A tricky question, but I would have said no, given the potential drug-drug synergism in one circumstance and not

another. So, I would say establish with monotherapy, and that's a separate, potentially related issue. So, I would say no for those reasons.

And beating the comparator in special populations? Again, I would say no; that is, that it would be the broad cross section of populations, but that clearly for orphan or special populations, a boutique drug, that might be relevant. So, that's the way I'd answer that.

DR. BORER: Does everybody agree with that? Are there any modifications? Doug.

DR. THROCKMORTON: Sorry. Paul, I just want to make sure I understand. Part of this had to do with sort of potential claims. What is it possible to get? And you can sort of think of some of these as being more significant. Say I was able to show you convincingly that I could beat not only a comparator, but a comparator plus another drug. Is that a more robust claim than just beating the comparator agent at one dose or however you arranged that?

The other 3.5 had another intent and that had to do with you could argue, some might argue, that this is a restricted population that was studied in this trial. That is, these trials were in mild to moderate hypertension. We've had some discussion this morning that there are other people out there, obviously, that have to

take these drugs monotherapy as opposed to combination therapy.

Are there other populations that a sponsor might, for whatever reason, choose to investigate and if done convincingly, the standard that you guys are talking about today that we've provided to sponsors in the past and brought that in, that that would be sufficient to get a claim that we are superior in Norwegians? You know, choose your population. If done well enough, are there populations you could identify that would be relevant for that kind of a claim? Norwegians, my apologies.

DR. ARMSTRONG: So, 3.4 and 3.5. Just to clarify then. Entirely reasonable against a background of a diuretic therapy that one agent might well be superior to another and that would be enough to establish a claim, absolutely, and clearly entirely reasonable to select an elderly population with renal dysfunction and suggest that under those circumstances, but not in the broad cross section, there would be evidence for superiority. So, absolutely yes.

DR. BORER: What about 3.3, Paul? I think that everybody probably would agree that 3.1, 3.2, 3.4, and 3.5 could give a basis for a superiority claim. But what about 3.3?

DR. ARMSTRONG: Sorry. I thought no.

DR. THROCKMORTON: I heard no.

DR. ARMSTRONG: I said no to that because I don't think you want to mess outside the approved dose range given a safety issue potential and other issues.

DR. THROCKMORTON: But I also heard, Paul, no for 3.4 and 3.5. Did I misunderstand?

DR. ARMSTRONG: Now that you've broadened the question and I've appropriately broadened my thinking, I have tried to reflect the answer.

DR. LORELL: I think that 3.5 is a very important question and not for consideration for the specific labeling that we're required to address today, but for the FDA in the future. We've already talked about an extremely important population that wasn't addressed in the study at all, and that's isolated systolic hypertension of the older patient, a very, very large group.

I think the concerns about non-white, non-caucasian populations, whether they be black or Hispanic Americans, remain a very major concern as a public health and as a labeling issue.

DR. CARABELLO: But for 3.5, we're only talking about studies which were specifically targeted to those populations, a study that proved that the drug was better in Sicilians, for instance, not where the subgroup analysis happened to show that Sicilians did better.

DR. BORER: I think the issue here is that Doug is asking us on what basis could one come forward and request a superiority claim and not what is absolutely necessary to have in every package in which a superiority claim is being made.

Bob.

DR. TEMPLE: This would more relate to cross-class comparisons, but it's completely obvious from data we already know about that it would not be difficult to show that certain drug classes work better in a black population than ACE inhibitors or AII blockers. In fact, there already are published trials saying just exactly that.

I hear you thinking that that might be useful information and would be legitimate to put into labeling if it was properly done and appropriately qualified?

DR. BORER: To put into labeling? I think if we had the information, it would be reasonable.

DR. TEMPLE: What we have now is labeling that says this drug works equally well in whites and blacks. You have that. You have other labeling that says this doesn't work very well in a black population. There isn't anything that I know about that says I work better than they do in a particular population. I may just not remember, but I don't think so.

DR. THROCKMORTON: It's all pretty general