UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIORENAL DRUG PRODUCTS

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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81ST MEETING

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THURSDAY, JUNE 26, 1997

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The Advisory Committee met in the Jack Masur Auditorium, Clinical Center-Building 10, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, at 9:00 a.m., Barry Massie, M.D., Chairman, presiding.

PRESENT:

BARRY MASSIE, M.D.	Chairman
JOAN C. STANDAERT	Executive Secretary
ROBERT CALIFF, M.D.	Member
JOHN DiMARCO, M.D.	Member
CINDY GRINES, M.D.	Member
MARVIN KONSTAM, M.D.	Member
JOANN LINDENFELD, M.D.	Member
LEMUEL MOYE, M.D., PhD	Member
DAN RODEN, MDCM	Member
UDHO THADANI, M.D., FRCP	Member
MICHAEL WEBER, M.D.	Member
RAYMOND LIPICKY, M.D.	FDA Representative
LILIA TALARICO, M.D.	FDA Representative

PRESENT: (continued)

SPONSOR REPRESENTATIVES:

DAVID ELLIS, M.D., PhD	Neurex
ROBERT LUTHER, M.D.	Neurex
VENDANA MATHUR, M.D.	Neurex
ADDISON TAYLOR, M.D., PhD	Neurex
EUGENE BRAUNWALD, M.D.	Rhone-Poulenc Rorer
MARC COHEN, M.D.	Rhone-Poulenc Rorer
GREGG FROMELL, M.D.	Rhone-Poulenc Rorer
JANET RUSH, M.D.	Rhone-Poulenc Rorer
MAX TALBOTT, PhD	Rhone-Poulenc Rorer

ALSO PRESENT:

SYLVAIN DURRLEMAN, M.D., PhD
CAROL FRANCISCO, PhD
ERIC GENEVOIS
MARK PERRONE, PhD

I N D E X

P R O C E E D I N G S

Time: 9:03 a.m.

CHAIRMAN MASSIE: I'd like to welcome to the 81st meeting of the Food and Drug Administration Cardiorenal Advisory Committee. We are going to consider two products today, in the morning fenoldopam, in the afternoon enoxaparin.

I haven't received any notice of public comment, but if there is anybody that wants to take advantage of the open public hearing, they should identify themselves now.

In the absence of that, let me proceed by first introducing the Committee members, and then having Joan read our usual waivers and so forth.

Starting on my right, we have Dr. Lem Moye, Dr. Dan Roden, Dr. JoAnn Lindenfeld, Dr. Robert Califf, Dr. Marvin Konstam, our Committee secretary--Executive Secretary, Joan Standaert, myself--I'm Dr. Barry Massie from University of California at San Francisco, and then continuing on: Mike Weber. Dr. Cindy Grines is not here, but we expect her, and Dr. John DiMarco, and Dr. Thadani is somewhere, but he's not here yet, and Dr. Ray Lipicky.

Why don't we proceed with reading of the waivers and conflicts of interest.

MS. STANDAERT: The following announcement addresses the issue of 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 and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting, with the following exception:

In accordance with 18 U.S.C. Section 208(b)(3), a full waiver has been granted to Dr. Udho Thadani which will permit him to participate in all matters concerning Corlopam. A copy of the waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Office, Room 12-A30 of the Parklawn Building.

Dr. Robert Califf is excluded from participation in all matters concerning Lovenox.

We would also like to note for the record that Dr. Robert Califf and his employee, the Duke University Medical Center, and Dr. JoAnn Lindenfeld and her employer, the University of Colorado, Health

Science Center, have interests which do not constitute financial interests in the particular matter within the meaning of 19 U.S.C. 208(a), but which could create an appearance of a conflict.

Doctors Califf and Lindenfeld have unrelated interests in sponsoring companies making competing products to Corlopam. The agency has determined, notwithstanding these interests, that it is in the best interest of the government to have Dr. Califf and Dr. Lindenfeld participate fully in all matters concerning Corlopam.

Furthers, Doctors Thadani and Grines were previously involved in the Essence study of Lovenox. Because of his past involvement, Dr. Thadani may participate in the discussions of Lovenox. However, he will be excluded from any voting related to Lovenox.

Since Dr. Grines' past involvement with respect to Lovenox was minimal, she may participate fully in all matters concerning Lovenox.

Lastly, we would like to note that Dr. Barry Massie was previously involved in the study of Nicardipine, a competing product to Corlopam.

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.

That concludes the conflict of interest statement for June 26, 1997.

CHAIRMAN MASSIE: Thank you very much, Joan. That's one of the shorter lists of waivers and conflicts that I've experienced during my time here on the Committee.

I think we can proceed on then to our sponsor's presentation of Corlopam or fenoldopam, and I'd like, if possible, for the Committee to let the sponsor's complete their presentation before we interrupt with questions unless there's some clarification of fact that just can't be delayed.

DR. LUTHER: Thank you, Dr. Massie, and good morning, ladies and gentlemen.

I am Bob Luther from Neurex Corporation, located in Menlo Park, California. We are pleased to present Corlopam or fenoldopam to the Cardiovascular

and Renal Drugs Advisory Committee this morning.

First slide, please.

I will introduce and close the formal presentations on fenoldopam, which will highlight three critically important clinical studies sponsored by Neurex. First, our pharmacokinetic, pharmacodynamic study will be presented by Dr. Addison Taylor. Second, Dr. David Ellis will present the malignant hypertension trial. Third, Dr. Vandana Mathur will present the renal function study.

Finally, Dr. Ellis will review the overall safety profile of intravenously administered fenoldopam. These presentations will be succinct, and I add the request that you hold questions until the conclusion of the presentations, if at all possible.

The following academic consultants are present representing Neurex: Dr. Murray Epstein from University of Miami, School of Medicine; Dr. Brian Hoffman from Stanford University School of Medicine; Dr. Jerrold Levy from Emory University School of Medicine; Dr. Suzanne Oparil from the University of Alabama at Birmingham; Dr. Jeremy Ruskin from Harvard Medical School; and Dr. Addison Taylor from the Baylor College of Medicine.

Other nonacademic consultants are also

present.

The chemical structure of fenoldopam mesylate is shown in this figure. Fenoldopam is a benzazepine mimetic of the native catecholamine dopamine, the structure of which is highlighted in white.

The catechol moiety of fenoldopam shown on the left is rapidly metabolized by COMT, as are other catecholamines, and FDA laboratories have shown conclusively that fenoldopam is not metabolized by cytochrome P-450.

Unlike dopamine, fenoldopam is a highly selective dopamine D-1 receptor agonist. Fenoldopam acts peripherally only, and has specific pharmacologic effects on the vasculature and the nephrons.

Fenoldopam was originally discovered by Smith-Kline & French and has been under clinical development for nearly 20 years. The preclinical and clinical experience with fenoldopam is extensive, and the scientific literature contains in excess of 1,000 articles on fenoldopam.

Fenoldopam was originally developed for the oral treatment of hypertension, chronic renal insufficiency, and congestive heart failure. Following an extensive clinical development program,

development of the oral product was discontinued by Smith-Kline Beecham in 1985 due to poor bioavailability and short plasma half-life.

Nevertheless, development of intravenous fenoldopam continued, and considerable experience in severe hypertension was generated. This broad base of experience is depicted in the next slide.

Smith-Kline & French conducted ten trials in severe hypertension with IV fenoldopam. The mean reductions in diastolic blood pressure with estimated 95 percent confidence intervals for each of these studies are graphically depicted in the slide.

These trials were conducted in the United States, Europe, Africa, and Asia. So heterogenous patient populations were studied, differing in ethnic origin and culture, geographical distribution, and standards of medical care and practice.

In addition, patients were studied in various hospital settings, including emergency departments, intensive and coronary care units, medical wards, surgical suites, and recovery rooms.

Despite all of this interstudy variability, a single common result emerged. Fenoldopam effectively, substantially, and predictably lowered blood pressure in patients with severe

hypertension.

The ten trials show mean reductions from baseline in diastolic blood pressure ranging from approximately 24 to 33 millimeters mercury, generally occurring at doses of 0.1 to 0.3 micrograms per kilogram per minute.

Two of these trials employed sodium nitroprusside as a comparator agent. Results from these trials are shown in pink, with fenoldopam represented by solid lines, and sodium nitroprusside by broken lines. The data indicate that both drugs reduced diastolic blood pressure equivalently.

In addition to these studies, fenoldopam was compared to nifedipine in a German study of post-operative hypertension. In this trial, blood pressure targets were achieved more quickly and more predictably with fenoldopam than with the calcium channel blocker.

Based on these trials, SK&F filed an NDA for intravenously administered fenoldopam in 1988, specifically for the treatment of malignant hypertension. In 1991 FDA issued a nonapprovable letter for IV fenoldopam, citing two critical deficiencies in the clinical database.

First, the relationship between

pharmacokinetics and pharmacodynamics had not been explored in the hypertensive patients. Hence, appropriate directions for use could not be written, because the dosing regimen had not been defined.

Second, the patient population studied had severe hypertension, and thus did not adequately support approval for the treatment of malignant hypertension, which was the indication requested by SK&F.

Given this history, Neurex licensed worldwide rights to fenoldopam in 1994. In consultation and collaboration with the Cardiovascular and Renal Drugs Division, Neurex designed a compact clinical program to address these two issues.

Two pivotal trials plus a renal function study have been conducted, and they will be presented in detail this morning. The pharmacokinetic/pharmacodynamic trial was designed as a pivotal investigation of multiple fixed doses of fenoldopam in hypertensive patients. Dr. Taylor will present the study.

A second pivotal study was designed to explore the safety and pharmacodynamics of multiple fixed doses of fenoldopam in patients with true hypertensive emergencies. Dr. Ellis will present the

results of this trial.

Finally, because the kidney is an organ subject to damage from both hypertension and hypotension, Neurex conducted a well controlled study of the effects of multiple doses of fenoldopam on renal function. This study specifically assessed the drug's effect on renal blood flow, which is the critical factor underlying renal ischemic injury. Dr. Mather will present this trial.

We believe the data presented this morning will convincingly demonstrate the following facets of the clinical profile of fenoldopam:

First, fenoldopam is well behaved pharmacokinetically with clear dose proportionality.

Second, the dose response curve is well defined and is qualitatively similar in significantly different hypertensive patient populations. The drug's blood pressure lowering effects are predictable with a low incidence of overshoot. Clear, data driven instructions for use can be written.

Third, the drug has a good safety profile and is well tolerated in patients with hypertension, including patients with and without evidence of acute, ongoing end organ damage.

Fourth, fenoldopam maintains or improves

renal blood flow, despite lowering systemic blood pressure. This is a critically important safety feature of the selective D1 receptor agonist.

The clinical data support the approval of fenoldopam for two distinct indications. The first indication is the short-term treatment of hypertension when oral therapy is not feasible or possible, including use in patients who are undergoing surgery or who otherwise cannot take medications by mouth.

The data also support the approval of fenoldopam for the treatment of patients with severe hypertension with or without evidence of acute, ongoing end organ damage, thus including patients with malignant hypertension.

Now I will turn the podium over to Dr. Addison Taylor, who will discuss dopamine receptor pharmacology and the pharmacokinetic/pharmacodynamic trial.

DR. TAYLOR: Thank you, Dr. Luther.

The fenoldopam clinical pharmacology presentation will focus on three distinct topics. First, we will consider dopamine receptor pharmacology as it pertains to fenoldopam's pharmacodynamic effects. Second, we will summarize pharmacokinetic and pharmacodynamic questions that remain unanswered

at the time the FDA issued the nonapproval letter for fenoldopam, and finally we will present the results of the first evaluation of the pharmacokinetics and the pharmacodynamics of fenoldopam administered as a fixed dose, constant rate, continuous intravenous infusion over 48 hours.

Fenoldopam is a selective dopamine-1 receptor agonist. It binds to postsynaptic dopamine D1B receptors in the mesenteric, coronary and renal vasculature that mediate basodilation, and it binds to the D1A receptors in the kidney and in the gastrointestinal tract that mediate natriuresis, gastrointestinal motility, respectively.

It does not bind to any of the family of D2 receptors, and it does not cross the blood/brain barrier. In addition, it does not interact with either alpha-1 adrenal receptors or beta adrenergic receptors, and thus does not mediate either basoconstriction or have a chronotropic effect.

At the conclusion of the drug development program for fenoldopam initiated by Smith-Kline & French, a number of pharmacokinetic issues had been addressed.

For example, the pharmacokinetic parameters following short term administration of

fenoldopam had been characterized, and comparable plasma concentrations of fenoldopam were noted in patients with and without hepatic or renal impairment, suggesting that during short term infusions, no changes in dose would be required. However, several critical questions remained unanswered.

The principle pharmacokinetic and the pharmacodynamic issues centered around the behavior of fenoldopam during prolonged infusions. Questions summarized on this slide, such as whether the time to achieve steady state, whether there was proportionality of steady state concentration to dose, and whether there were time dependent changes in steady state plasma concentrations during prolonged fixed dose infusions of fenoldopam remain to be answered.

Since fenoldopam is a racemate with predominant pharmacodynamic effect attributed to the R enantiomer, it was not known if there were important differences in the pharmacokinetics of the two enantiomers that may influence the pharmacodynamic profile of fenoldopam or whether there were time dependent changes in metabolism and/or the clearance of the enantiomers.

Finally, pharmacokinetic parameters, after

stopping infusions of fenoldopam after prolonged administration, had not been characterized.

Smith-Kline & French performed a variety of pharmacodynamic studies, but their design was primarily titration to effect in nature. The pharmacokinetic and pharmacodynamic profiles and interrelationships during fixed dose, constant rate IV infusion were not defined, and there was very little information about either onset or offset of drug effect during prolonged infusions. In addition, questions about tolerance and rebound had not been addressed adequately.

To guide the design of a blinded, fixed dose infusion trial, an initial pilot study was done. The study employed open-label, nonrandomized dosing with exactly the same protocol as was subsequently used in the blinded, randomized, definitive, fixed dose trial.

Adverse cardiovascular effects that occurred at high, fixed dose infusion rates, specifically above 1 microgram per kilogram per minute, during the pilot study served to define the maximum tolerated dose. We found that the mechanics of the protocol, while very rigorous, could be successfully carried out.

Therefore, we designed the definitive trial with a focus on the measurements of the pharmacokinetic profiles of the racemate, fenoldopam, and its enantiomers during and after a 48 hour infusion.

The pharmacodynamic issues that were evaluated during this trial included the time to peak effect, the maximum tolerated infusion rate, and whether or not the hemodynamic effects were maintained or tended to decline during prolonged infusions.

Finally, did the hemodynamic response to the drug behave predictably after discontinuation of the infusion and, most importantly, did a dose response relationship exist between the pharmacokinetics of fenoldopam and its hemodynamic effects?

The design for this randomized, double blind, placebo controlled PK PD trial is shown on this slide. An initial outpatient evaluation and enrollment period included a mandatory withdrawal from all drugs and basoactive agents for at least ten days.

Patients with supine diastolic blood pressures between 95 and 119 millimeters of mercury in the clinic were then admitted for a four-day in-patient study, which included vehicle infusions on

days one and days four, and infusion of either placebo or one of four doses ranging from 0.04 to 0.8 micrograms per kilogram per minute on days two and days three.

Blood pressure and heart rate were measured every 15 minutes or more frequently throughout the 96-hour trial, with a noninvasive, automated blood pressure measuring device. On day two patients had to have a supine diastolic blood pressure of 90 millimeters of mercury in order to quality for randomization to placebo or to active drug.

The demographics of the patients enrolled in this multi-center trial are summarized here. Three different study institutions enrolled a total of 33 patients, 32 of whom completed the trial. One patient failed to complete, not because of an adverse effect from fenoldopam, but because of limited intravenous access.

The mean age was approximately 50. Approximately 25 percent of the study's subjects were African American. The majority were male, and the mean screening diastolic blood pressure was 99 millimeters of mercury.

Let's focus first on the pharmacokinetics of fenoldopam. The plasma concentrations of racemic

fenoldopam as a function of time are shown on this slide. Samples for plasma fenoldopam measurements were obtained at frequent intervals during the first hour of infusion, then hourly for the next five hours, and then every six hours for the termination of the 48-hour infusion.

At the completion of infusion, samples again were frequently collected to evaluate the offset pharmacokinetics of the drug. The data clearly demonstrate dose proportionality between fenoldopam dose or infusion rate and plasma concentration.

For example, the plasma fenoldopam concentrations for patients receiving the highest dose in this trial, namely 0.8 mcgs per kilogram per minute or approximately 30 nanograms per mil, and the plasma concentrations for patients receiving 0.4 mcgs per kilogram per minute are approximately 15 nanograms per mil.

In fact, linear dose proportionality holds throughout the entire dose range studied. The calculated elimination phase terminal half-life was 4.6 minutes, with a confidence interval of 3.8 to 6.3 minutes. The plasma clearance was approximately 28 ml per minute per meter squared, and the volume of distribution at steady state was approximately 17

liters.

Although not shown, the pharmacokinetic parameters for R-fenoldopam, the active enantiomer, analyzed for patients receiving 0.4 and 0.8 micrograms per kilogram per minute were similar to those for the racemate.

One of the principle goals of this study was to look at onset and offset pharmacokinetics, and we have expanded the time scale on this slide in order to visually facilitate that assessment.

Plasma steady state fenoldopam concentrations are generally achieved between 30 minutes and one hour, consistent with the half-life of approximately five minutes. Similarly, consistent with the short half-life, fenoldopam plasma concentrations declined rapidly upon discontinuation of infusion.

Shown on this slide are pharmacokinetics which include the mean systolic and diastolic blood pressures on the lefthand ordinate, and plasma fenoldopam concentrations on the righthand ordinate versus time for patients that received the highest dose in this study -- that is, 0.8 micrograms per kilogram per minute.

Plasma concentrations during and after

infusion are those shown on the previous two slides. A large number of hemodynamic data points were collected, and the mean systolic and diastolic blood pressure values are plotted here.

During the first day of the study when vehicle was infused, the expected circadian variation in both systolic and diastolic blood pressure was observed. When drug infusion was initiated on day two, the plasma concentration for fenoldopam rose promptly, and there was a concurrent prompt reduction in both systolic and in diastolic blood pressure, which is maintained over the 48 hours of infusion.

These data show that the circadian variation in blood pressure remains apparent, despite substantial drug induced decreases in systolic and diastolic blood pressure. When the infusion of fenoldopam is discontinued, blood pressure rises toward the baseline.

This graph of heart rate and plasma fenoldopam concentrations is constructed similarly to the previous slide. Following the start of fenoldopam infusion, heart rate increases promptly and concurrently with the reduction in systolic and diastolic pressure shown on the previous slide.

The brisk increase in the heart rate is

probably compensatory, given the fact that this is a D1 receptor agonist that promotes direct basodilation.

While the data show that heart rate remains elevated during the entire 48 hour infusion period compared to the baseline, peak heart rates occur early, and they are not maintained throughout the first 24 hours of infusion. In fact, they begin to decline during the second 12 hours of the first 24 hour period, and are maintained at a much lower level during the second 24 hours of infusion than during the first 24 hours of infusion. Upon discontinuation of fenoldopam, the heart rate slowly returns toward the baseline.

The next three slides summarize the effects of fenoldopam on diastolic blood pressure, systolic blood pressure, and heart rate, displayed by dose at six time points, specifically one, four, 24, and 48 hours during infusion, and four and 24 hours following discontinuation of drug infusion.

At one and at four hours, fenoldopam induces well behaved, dose related reductions in diastolic pressure. The magnitude of these changes is diminished at 24 hours, and even smaller at 48 hours.

Twenty-four hours following discontinuation of the drug, diastolic pressure has

returned toward baseline, without overshoot.

The next slide depicts changes in systolic blood pressure similar to those shown on the previous slide for diastolic blood pressure. Again, the peak effects of the drug tend to occur at one and at four hours, with a gradual diminution in effect at 24 and 48 hours, and again compared to the placebo effect, there was very little residual effect on systolic blood pressure 24 hours after discontinuation of the drug.

Heart rate again shows a monotonic, dose related increase in heart rate, which is maximal again between one and four hours, with a reduced heart rate response at 24 and almost no heart rate response at 48 hours except in patients at the two highest doses, .4 and .8 micrograms per kilogram per minute. There is again some maintenance of reflex tachycardia in the two highest dose groups 24 hours after drug infusion.

So in summary, we can say from this study that the pharmacokinetics confirmed the original observations of the Smith-Kline & French database, suggesting a short half-life of approximately five minutes. There as rapid attainment of steady state concentrations of the drug at approximately 30 minutes.

There was proportionality between dose or infusion rate and plasma concentrations of the drug, without any pharmacokinetic alterations in either the racemate or the R enantiomer for fenoldopam over a 48 hour period of infusion. There was rapid elimination of the drug upon discontinuation of drug infusion.

Pharmacodynamically, the effect on blood pressure and heart rate were predictable. They were rapid in onset, and they were in fact proportional to dose. There was the appearance of gradual tolerance, although there was always maintenance of effect throughout the 48 hour period of time, and there was no evidence of rebound hypertension upon discontinuation of the drug.

Dr. Dave Ellis will now talk about efficacy in the 06 trial.

DR. ELLIS: Thank you, Dr. Taylor.

The Neurex trial in hypertensive emergencies was designed to confirm the pharmacokinetic and pharmacodynamic findings from the trial that Dr. Taylor has just presented.

This trial is different from the earlier Smith-Kline & French trials in that the evidence of acute onset, ongoing end organ damage was required for entry into the study. The entry diastolic blood

pressure had to be at least 120 degrees mercury.

The Neurex trial is a randomized, double blind study comparing four different infusion rates of fenoldopam, specifically 0.1, 0.3, .1 and .3 micrograms per kilo per minute. The lowest dose was chosen as a minimally effective comparator dose, as we were advised by numerous investigators and IRBs that it would be considered unethical to use a placebo in this patient population.

The fixed dose, constant rate infusion was to last for a full 24 hours, with transfer to oral medication allowed after 18 hours. Importantly, the protocol also specified the investigators were to maintain the infusion constant for the first four hours, if at all possible, and for the complete 24 hour period, if the patient was adequately controlled.

We did allow a maximum of two up titration steps after the first hour, but with the blind maintained for at least through the first four hours, and for the full 24 hours, if possible.

Our primary endpoint was reduction in diastolic blood pressure at four hours, and our main statistical comparison was versus the lowest dose group.

This next slide gives a brief summary of

the patients that were enrolled. They were balanced for demographic parameters with no important differences in the basic demography between the four treatment groups. The median age was 45 years, with 55 percent of the patients being male. Seventy-eight percent of the patients were African American. The mean baseline blood pressure was 208 over 134.

This slide summarizes the protocol specified end organ damage, as required by the protocol. You can see that 65 percent of the patients met neurological criteria. Thirty-nine percent met cardiovascular criteria; 35 percent met renal criteria, and 35 percent met one or more ophthalmological criteria. Overall, 99 percent of the patients had at least one of these protocol specified entry criteria.

There are two possible concerns about the protocol specified criteria. One is that some of the criteria were subjective, not objective, such as headache; and two, some of the criteria may have been satisfied by chronic rather than acute end organ dysfunction. Most notably elevated BUN and creatinine.

To investigate this issue in more detail, all trial data were reviewed by a physician for

objective evidence of acute end organ damage. Patients were classified as meeting objective criteria for definite probable or possible malignant hypertension.

Based on this analysis, almost 70 percent of our patients were found to have convincing evidence of malignant hypertension.

About half of the study patients had taken no antihypertensive medications during the week preceding entry into the trial. Twenty percent of the patients had a history of substance abuse, either alcohol or cocaine, primarily. Eighty-two percent of the patients had left ventricular hypertrophy at baseline, and 17 percent had a history of heart failure. Baseline electrocardiograms in 17 percent of the patients showed evidence of an old myocardial infarction.

Another point of interest is that 20 percent of the patients had clonidine withdrawn at some point during the week prior to the entry into the trial.

Of the 89 patients who were treated for at least four hours, 74 were able to be treated for the entire 24 hours. Of those 15 patients who discontinued between four and 24 hours, two terminated

secondary to adverse events, and 11 patients discontinued because their blood pressure was controlled, and not because of any adverse events.

In addition, one patient was designated a treatment failure, and one patient needed to receive a prohibited medication.

Only one patient was unblinded during the first four hours, and 76 percent of the patients were able to stay on their randomized, fixed dose up titration for the remaining patients.

The highest rate of up titration was in the low dose group, whereas 87 percent of the high dose were able to stay on that dose for the first four hours. While this trial was not designed to formally assess pharmacokinetics, a limited number of blood samples were drawn to assess steady state plasma concentrations.

The data showed the steady state plasma concentrations for fenoldopam in this study were comparable to those observed in the formal PK PD study.

The primary efficacy endpoint was the mean change from baseline in diastolic blood pressure at four hours, and the statistical comparison is with the reduction from baseline in the low dose group -- that

is, the group receiving .01 micrograms per kil per minute.

Please note several points from this graph. First, there is a very nice monotonic order in both the rate and depth of the reduction in diastolic blood pressure versus dose. The highest dose shows the most rapid decline, and also declines more than the three lower doses.

These results are highly significant, with a difference between the high dose group and the low dose group at four hours, having a p value of .0001. The second highest dose group -- that is, .1 micrograms per kilo -- was also significant, and there was a trend toward significance for the .03 group as well.

Looking at the results for systolic blood pressure, you see the same prompt rate of blood pressure decrease during the initial part of dosing, and again you see a reasonable dose response, and once again the difference between the highest and lowest dose groups is highly significant.

This slide shows the heart rate for the first four hours. Again, you see a dose response where the greatest effect is at the highest dose. The heart rate seems to peak from between two and a half to four

hours.

Given the depth of blood pressure lowering, increase in heart rate in the .1 dose group is quite small, and this fact weighs heavily in our dosing recommendations.

Earlier studies by Shusterman, et al., using -- in the Smith-Kline & French experience have allowed some inferences regarding whether renal dysfunction altered fenoldopam's antihypertensive effect. In that study patients were stratified into those with creatinine clearances greater or less than 70 milliliters per minute.

As seen on this slide, baseline blood pressure was elevated to similar levels in both treatment groups, and two groups required about an equal dose of fenoldopam to reduce blood pressure to about the same level, suggesting that renal dysfunction did not affect fenoldopam antihypertensive efficacy.

We also attempted a similar analysis in our malignant hypertension trial by stratifying patients using a cutoff of serum creatinine greater than 2.4 milligrams per deciliter. In this analysis, the more renally impaired patients also had more severe blood pressure elevations. Consequently, it

was not possible to discern whether the higher fenoldopam dosing needed was attributable to renal dysfunction or to more severe hypertension.

A final data analysis is the comparison of the pharmacodynamic effects of fenoldopam in the mild to moderately hypertensive patients studied in the PK PD trial with the hypertensive emergency patients studied in the present trial.

This slide compares side by side the mean percent reduction in diastolic blood pressure for the two trials. Only the 0.1 dose was common in the two trials, but the .03 and .04 doses and the .3 and .4 groups were considered close enough for comparison.

The dose response is clearly evident in both populations. At the two lower doses the pharmacodynamic effect is somewhat less in the mild to moderate patients, but at the high dose group the effects are practically identical.

We conclude that the pharmacodynamics of fenoldopam are qualitatively similar in a wide variety of hypertensive patients.

In conclusion, over 500 patients have been studied in the severe hypertension trials conducted by SFK and Neurex, and a wide variety of patients have been studied, both in terms of entry criteria and

ethnic background.

There has been a good representation of black and Asian patients in this population, as well as female patients.

The effects of fenoldopam have been consistent. The onset of activity has been rapid. The rate and magnitude of blood pressure lowering are dose dependent, and there is no evidence of overshoot or rebound, and the effects of the drug are predictable in this patient population.

I would now like to turn the podium over to Dr. Vandana Mathur who will describe our renal studies.

DR. MATHUR: Thank you, Dr. Ellis. Good morning, ladies and gentlemen.

Dr. Ellis has just concluded that fenoldopam effectively lowers blood pressure. I would like now to turn your attention from the systemic hemodynamic effects of fenoldopam to its renal hemodynamic effects. I trust that, by the conclusion of my presentation, I will have convinced you that fenoldopam maintains or improves renal blood flow, despite lowering blood pressure.

This is a critical safety feature of this dopamine receptor agonist. I will start out by

summarizing the Smith-Kline & French hypertension studies which also studied renal function, addressing in particular blood pressure, glomerular filtration, and renal blood flow.

Second, I will review a Neurex renal function study which was the first renal function study to demonstrate dose responsiveness of renal blood flow.

Finally, I will review an independent renal function study by Doctors O'Connell, Carey, et al..

Smith-Kline & French conducted five hypertension studies which included 77 patients with various degrees of hypertension, who additionally had renal function measured. Two of these studies were placebo controlled. Two were positively controlled with sodium nitroprusside, and one was uncontrolled.

The magnitude of blood pressure reduction in these studies is shown in the slide. Each different colored line represents an individual trial. Where sodium nitroprusside controls were performed, these are additionally shown.

As you can see, the systolic blood pressure, shown on the left, declined by anywhere from ten to 40 millimeters of mercury, while the diastolic

blood pressure declined anywhere from ten to 30 millimeters of mercury in these studies.

Despite the magnitude of reduction of blood pressure in these studies, treatment with fenoldopam increased renal plasma flow from baseline in each of the studies in which this variable was measured. This is shown here.

Additionally, these flat lines represent a sodium nitroprusside control and a placebo control, indicating that in the controls there was no increase in renal plasma flow.

The glomerular filtration rate from these studies is shown in this slide. Across the bottom are the individual study numbers. Again, where control information is available, this is additionally shown. Both the baseline and on-treatment glomerular filtration, along with 95 percent confidence intervals, are graphed.

Examination of the mean data at overlapping confidence intervals strongly suggests that there are no statistically significant changes in GFR with fenoldopam.

Because the majority of these studies were open label and were not placebo controlled relationships of fenoldopam on renal function, an

additional renal function study was conducted by Neurex. The overview of this study is presented in the following slide.

The objective of the study was to study the relationship of renal plasma flow to fenoldopam dose. Fourteen normal males were studied. This was a randomized, placebo controlled, double blinded trial. Patients were crossed over from a low sodium to a high sodium diet or vice versa.

Patients received escalating, sequential, fixed dose infusions of 03, 0.1, and 0.3 micrograms per kilo per minute. This dose range was selected to overlap the dose ranges that were used the PK PD in the malignant hypertension studies.

The primary outcome variables were renal plasma flow, a surrogate for renal blood flow measured by PAH clearance, glomerular filtration rate as measured by inulin clearance, electrolyte excretion, and hormone levels.

In this population of normotensive individuals, systolic blood pressure did not decrease. However, diastolic blood pressure decreased in a dose dependent manner relative to placebo. These differences were statistically significant at the two highest dose groups.

Because the state of sodium balance did not influence the results of this trial, only the overall results, independent of sodium state, are presented for clarity. The main results from the study are presented on the following slide.

Here on the left ordinate is the PAH clearance, a marker for renal plasma flow. On the righthand side are the fenoldopam plasma concentrations, and across the bottom are the increasing infusion rates of fenoldopam.

As you can see, fenoldopam increased renal plasma flow in a dose dependent manner, and this was statistically significantly different from placebo. In addition, the increase in renal plasma flow monotonically was predicted by the increasing plasma levels of the drug, shown here in the blue boxes.

As was seen previously, glomerular filtration was unaltered by administration of fenoldopam.

I will now switch gears and discuss an independent renal function study conducted by Doctors O'Connell, Carey, et al., at the University of Virginia, recently published in Hypertension. The objective of this study was to determine is a proximal tubule dopamine-1 like receptor defect is present in

human essential hypertension.

This was a randomized, double blinded, placebo controlled crossover study. Thirteen normal subjects and 11 patients with salt sensitive hypertension with diastolic blood pressures in the 95-114 millimeters of mercury range were studied.

Salt sensitivity here was defined by a reduction in mean arterial pressure by greater or equal to 7 millimeters of mercury when switched from a 300 mil equivalent to a 10 mil equivalent per day sodium diet.

Patients received sequential, escalating, fixed dose infusions of between .001 and 0.2 micrograms per kilo per minute. At the highest infusion rate of between 0.1 and 0.2 micrograms per kilo per minute, both systolic and diastolic blood pressure in the hypertensive patients decreased by approximately 10 millimeters of mercury, and this was significantly different than what was seen in placebo.

In the normotensive individuals at this very dose, systolic blood pressure did not change. However, the diastolic blood pressure decreased by four to five millimeters of mercury, and this was also statistically significant relative to placebo.

The renal plasma flow is shown here. Both

the baseline and on-treatment values are shown, both for fenoldopam and for placebo, both in the hypertensive and in the normotensive population. As you can see, compared with placebo, fenoldopam increased the renal plasma flow, both in the hypertensive and in the normotensive population.

Again, as was seen in the Neurex study and the SKF studies, there was no change in glomerular filtration.

The SKF database, the Neurex renal function study, and the independent study by Doctors O'Connell and Carey all point to the same conclusion. Fenoldopam increases or maintains renal plasma flow, and maintains glomerular filtration while lowering systemic blood pressure. This strongly suggests that the drug is unlikely to compromise renal function when used for blood pressure control.

Maintenance of renal profusion and function during blood pressure lowering is a critically important pharmacologic and safety feature of this dopamine-1 receptor agonist.

I will now turn the podium back over to Dr. Ellis who will discuss additional safety features of fenoldopam.

DR. ELLIS: Thank you, Dr. Mathur.

The following points will be covered in this safety overview of fenoldopam. First, I will present the number of patients that have been exposed to fenoldopam. Second, I will review the adverse events in general and focus on the serious nonfatal adverse events, especially those that may be related to end organ compromise.

Next I will summarize all deaths that have occurred in the entire experience with intravenous fenoldopam, including both SKF and Neurex sponsored studies. Finally, I will review the electrocardiographic data.

Much of the safety data to be reported will be in the most severely ill patient population with severe or malignant hypertension, which is a stringent test of safety.

This slide summarizes the entire clinical experience with intravenous fenoldopam. The majority of the experience is derived from Smith-Kline & French trials. As you can see, a variety of indications have been studied, with a strong emphasis on hypertension.

The total of 1,009 patients have been treated with IV fenoldopam. In addition, 258 healthy subjects have also received IV fenoldopam.

This slide summarizes the adverse events

from the entire clinical experience with intravenous fenoldopam in patients. Most of the adverse events are those that you would expect of a vasodilator or as a result of the underlying disease.

Headache has been consistently the most frequently reported adverse event, with flushing, nausea and hypotension the next most frequently reported. In the Neurex trials the adverse event profile parallels the experience in the total population.

This slide summarizes the adverse events reported in the two trials which included sodium nitroprusside as a positive control. The total number of patients exceeds 200. This comparison confirms that the patterns of adverse events are quite comparable with fenoldopam and sodium nitroprusside.

Many of these events are likely to be due to the underlying disease itself or secondary to the effects of significant vasodilation.

This slide summarizes all of the serious nonfatal adverse events that were considered possibly or probably drug related from the combined Neurex and SK&F clinical experience.

There were 23 nonfatal serious adverse events in this combined database, and 18 of the 23

were related to the cardiovascular system. All of these conditions resolved satisfactorily with discontinuation of drug and/or treatment.

Not surprisingly, hypotension is the most common serious adverse event on this list. T-wave inversion was a frequently reported serious adverse event, especially in the early clinical trials. These T-wave abnormalities have been recognized with other antihypertensive agents, and were not associated with an increased incidence of angina pectoris, myocardial infarction or arrhythmias.

Most of the other adverse events were those that would be expected in a seriously ill patient population. Six of these events occurred in patients in the SK&F studies in heart failure, hepatic disease or renal disease.

A total of 19 deaths occurred in the total experience of 1,267 patients and subjects exposed to fenoldopam. This figure includes all deaths, regardless of causality attribution. Only two of these deaths occurred in the hypertension studies. The other 17 were in congestive heart failure, eight cases, renal disease, five cases, cardiac transplant, two cases, and other serious illnesses, three cases.

The two deaths that occurred in

hypertension studies both occurred off therapy and were clearly not related to drug. One was a presumed aortic dissection that occurred one week after the trial. The other was an intracerebral hemorrhage that occurred ten days after therapy was discontinued in a patient with a history of cerebral infarction.

The largest proportion of the deaths, eight cases, were in congestive heart failure trials and were primarily due to worsening of the heart failure. Of the eight heart failure deaths, seven occurred after the trial was completed. The one death that occurred on therapy in these CHF studies was a patient who died from ventricular fibrillation.

The patient had New York Heart Association Class IV heart failure and a low output state with a cardiac index of 0.8. The patient experienced sudden ventricular fibrillation on therapy and was successfully defibrillated. After the infusion was terminated, ventricular fibrillation recurred twice with an ultimately fatal outcome.

Unfortunately, electrocardiograms cannot be retrieved for this patient who was studied over eight years ago in South Africa.

The other two patients who died on therapy were suffering from cardiac transplant rejection.

These deaths were not regarded by the investigators as related to the drug.

A point of interest in these trials involving severely hypertensive patients with compromised cardiovascular, cerebral and renal vascular beds is the lack of occurrence of either deaths or serious adverse events thought to be secondary to the acute lowering of blood pressure.

In terms of cardiovascular complications, there were no deaths due to the study drug in the severe hypertension trials. Likewise, there were no myocardial infarction in all 11 of the trials in severe hypertension or hypertensive emergencies.

There were three cerebral vascular events in the hypertension trials, none of which were ischemic strokes. Two were intracerebral hemorrhages in SKF trials, and the third event was a subarachnoid hemorrhage in our hypertensive emergency trial.

The subarachnoid hemorrhage was due to radiographically documented rupture of cerebral arterial aneurysms and occurred nine days after the conclusion of the trial.

One of the intracerebral hemorrhages occurred ten days after the trial in a patient with a previous stroke who was being treated with heparin.

The other case of intracerebral bleeding occurred on therapy in a patient with two prior strokes. CT scanning documented a small temporal hemorrhage.

These events are unlikely related to fenoldopam, as the patients had known cerebral vascular compromise, and a hypertensive agent is much more likely to induce an ischemic stroke secondary to hypertension and poor cerebral profusion than a hemorrhagic event which is generally related to high blood pressure. There were no on-therapy deaths in the hypertension experience.

The pharmacokinetic/pharmacodynamic characteristics of fenoldopam facilitate the transition to oral therapy. The lack of rebound effects as demonstrated in the PK PD trial, allows the infusion to be turned off abruptly, if desired.

Likewise, the short half-life of fenoldopam ensure the rapid disappearance of the drug from the plasma. Two strategies have been used successfully for the transition to oral medications in the hypertensive emergency trial, either the addition of oral medication while the fenoldopam infusion was ongoing, somewhere between 18 and 24 hours, or discontinuation of the fenoldopam infusion with a subsequent addition of oral therapy.

Both strategies have been used successfully and, since there were no specifications in the protocol regarding oral therapy transfer, investigators used a wide variety of drugs for the ambulatory treatment of their patients.

This bar chart shows the actual timing of transfer to oral medications with respect to the discontinuation of infusion. Time zero indicates the time of discontinuation of the fenoldopam infusion. The negative numbers are hours before the end of infusion, and the positive numbers are hours after the infusion had been stopped.

The stack graph displays the addition of both diuretic and non-diuretic hypertensive agents. Most investigators chose to add oral drugs either before or right at the time of discontinuation of fenoldopam. Only a relatively few added oral drug therapy after discontinuation of fenoldopam.

This slide summarizes the drugs to which the patients were transferred at the end of the trial. Calcium channel blockers and ACE inhibitors were the most frequently used, followed by vasodilators and alpha beta blockers, most notably Lobetolol.

Interestingly, beta blockers were used sparingly, perhaps because of the preponderance of

African Americans in this trial.

Now shifting to the safety question that the Division has addressed to the committee, namely, the possible prolongation of a QTc interval.

In the SK&F uncontrolled severe hypertension trials, a mean prolongation of the on-therapy QTc interval of about one to two percent was observed. In order to investigate this finding in more detail, we have reviewed those studies where we have the actual electrocardiograms.

We used an expert centralized reader for this review. Specifically Dr. Galen Wagner of Duke University read all of the electrocardiograms in a blinded fashion. Three trials were reviewed, SK&F study number D1101 in severe hypertension that was controlled by sodium nitroprusside, and the two Neurex studies, our PK PD study in mild to moderate hypertension and our trial on hypertensive emergencies. Thus, we have data for patients with mild to moderate, severe, and malignant hypertension.

This slide summarizes the pertinent QTc data for the three trials reviewed. The mean change from baseline in the QTc interval at six hours on therapy is calculated for each of the treatment groups in the three trials.

In addition, three different threshold analyses have been done to identify patients who had pre-defined on-therapy prolongations of the QTc interval. The threshold criteria to identify outliers were: The QTc interval of greater than 500 milliseconds; prolongation of the interval by 50 or more milliseconds; and an increase in the QTc interval by ten or greater percent.

The QT intervals in the mild to moderate trial and the severe hypertension trial were determined by Dr. Wagner. In the hypertensive emergency trial the QT intervals were machine read.

In the mild to moderate severe hypertensive patients there were no patients that met any of these threshold criteria. Although the .8 dose group had the greatest increase in the mean QTc interval, there was no consistent dose relationship.

Analysis of the hypertensive emergency patients revealed four patients that exceeded one or more threshold criteria, but again there was no relationship to dose. Likewise, the mean change in the QTc interval ranged from -2 to +2 percent, with no apparent relation to dose.

Finally, the nitroprusside control trial in severe hypertension indicates that the same number

of patients met one of the prolongation criteria in each of the two treatment groups. The range of prolongation of QTc interval on therapy is again about one to two percent, with sodium nitroprusside being somewhat greater.

There were no episodes of ventricular tachycardia or sudden death in the hypertensive population. One patient in the hypertensive emergency trial experienced a near sinkable episode. She was unmonitored at the time, but the event was not thought by the investigator to be arrhythmic in etiology, and her symptoms did not recur.

In the heart failure studies involving 167 patients, three episodes of ventricular tachycardia were reported. The data describing these events makes no comment about the characteristics or duration of the ventricular tachycardia. However, these events were not associated with a cardiac arrest or sudden death.

In conclusion, the data substantiate a good safety profile for intravenous fenoldopam. There is a significant clinical database of over 1,000 patients, and the drug has been well tolerated by the majority of patients.

The adverse events that we have seen are

mostly exaggerated pharmacological effects or secondary to the underlying disease. The lack of evidence for end organ compromise is likewise gratifying. There have been no heart attacks or deaths on therapy in the hypertensive population.

Most of the deaths that have been reported have been due to the underlying disease state. There have been no unexpected laboratory abnormalities. The QTc interval changes observed in the severe or malignant hypertensive populations are not dose related and, with the exception of one patient with a near sinkable episode of unknown etiology, have not resulted in clinical sequelae.

The well behaved pharmacokinetic and pharmacodynamic properties of fenoldopam make it quite feasible to use noninvasive blood pressure monitoring for this drug, and interarterial monitoring was not utilized in our trials of fenoldopam, and is not recommended.

Likewise, the lack of rebound hemodynamic effects and the short half-life of fenoldopam allow a safe transition to oral therapy.

I should now like to turn the podium back to Dr. Luther.

DR. LUTHER: The previous speakers

presented data establishing that the pharmacokinetics of fenoldopam are well behaved and are correlated with the drug's pharmacodynamic effects, and that fenoldopam effectively and predictably lowers blood pressure in severely hypertensive patients, with and without evidence of acute, ongoing end organ damage, including patients with true hypertensive emergencies, and that fenoldopam has a good safety profile.

Based on the collective data from the two pivotal studies presented today, the recommended usual starting dose of fenoldopam is 0.1 micrograms per kilogram per minute. This dose is recommended, because it produces a rapid hypotensive effect of substantial magnitude, but does not significantly increase heart rate.

If in the treating physician's judgment a greater or lesser rate and/or magnitude of blood pressure response is required, a more aggressive or less robust starting dose may be used. Dosage may be adjusted to achieve targeted blood pressure reductions.

Dose titrations, if necessary, are recommended at minimum intervals of 30 minutes, based on the most rigorous pharmacokinetic data available, those presented by Dr. Taylor. Based on the

pharmacodynamic data in the malignant hypertension trial presented by Dr. Ellis, somewhat longer intervals between dose adjustments may be appropriate.

Neurex believes the clinical database for fenoldopam supports product approval, and the following label considerations. First, fenoldopam is indicated for the short-term treatment of hypertension when oral therapy is not feasible or possible, including use in patients who are undergoing surgery and who otherwise cannot take medications by mouth.

Second, the data support approval for the treatment of patients with severe hypertension with or without evidence of acute, ongoing end organ damage, including patients with malignant hypertension.

Third, the renal pharmacology of fenoldopam should be described appropriately in the labeling.

In closing, fenoldopam offers significant clinical advantages and benefits compared to currently available parental antihypertensive agents. Fenoldopam is easy to use and produces rapid and predictable lowering of the blood pressure in a dose dependent manner without overshoot or rebound, and the offset of effect is prompt.

The drug has a short plasma half-life of

approximately five minutes. This assures rapid attainment of steady state plasma levels, rapid clearance of the drug upon discontinuation of infusion, and ease of titration.

The pharmacokinetics of fenoldopam are very well behaved and linear, and fenoldopam does not interact with cytochrome P450 as shown by FDA. In addition, the initial starting dose of fenoldopam is well defined, and is similar in various patient populations and need not be adjusted for preexisting renal or hepatic disease.

Finally, fenoldopam has a good safety profile without evidence of end organ compromise.

Ladies and gentlemen, thank you very much for your attention. We stand prepared to answer your questions.

CHAIRMAN MASSIE: Thank you very much. I think we'll open up our questions first with our primary reviewer, Mike Weber, and then I think, since there's been so much on pharmacokinetics, maybe ask Dan Roden if he has any questions before going through the rest of the panel.

DR. WEBER: Well, thank you very much, Barry.

I wanted to start by getting back to the

data presented by Dr. Taylor. When I was reading some of the basic properties of fenoldopam beyond its actions at the D1 receptor, there was some discussion that it might have some effects on -- modest effects on adrenergic receptors, I think, especially the alpha 2 receptor.

Do you have any evidence or data concerning possible effects of the drug on endogenous catecholamine mechanisms where there were any changes in norepinephrine levels during treatment, whether there were any changes in endogenous catecholamine or sympathetic mechanisms?

The reason I'm asking, obviously, is because if the drug were governing the re-uptake of norepinephrine in some way or its release, then that might play a part in inquiring about possible rebound phenomena, which I want to get to a little later, especially in people with more severe hypertension.

DR. TAYLOR: The simplest answer, Mike, is that --

CHAIRMAN MASSIE: Could you come to a microphone?

DR. TAYLOR: The most straightforward answer, Mike, is that none of the Neurex studies examined endogenous plasma catecholamine

concentrations. There were limited studies in the Smith-Kline database that did look at catechols, and not unexpectedly, there is a fairly predictable increase in plasma norepinephrine concentrations, but of course, this drug, having postsynaptic effects and being a direct acting vasodilator, is likely to induce reflex increases in sympathetic activity anyway, which has made the attempt to estimate its effect as an alpha-2 agonist presynaptically very difficult.

Looking at the magnitude of the tachycardiac effects, especially at the higher doses, one can imagine that that's an overriding feature which makes whatever modest effect this drug may have at the alpha-2 receptor a little bit difficult to sort out.

DR. WEBER: You know, one of the interesting things you pointed out from the study you presented, the 005, was that there was some residual tachycardia, especially at the higher doses, several hours after the -- Is this my third mike? That's funny. I can hear myself very well.

There was some residual tachycardia even quite a few hours after the cessation of the doses, especially the higher doses. I was wondering, do you have -- Clearly, this was not now a reflex response to

a drop in blood pressure or at least it didn't seem to be that to me.

So can you think of any mechanism that might be affecting heart rate at that point? Of course, I'm thinking now just as a safety issue. Are there patients who may be susceptible to some kind of a tachy arrythmia, even fairly late in the infusion?

DR. TAYLOR: With regard to arrhythmias, these people -- and I can speak directly to those evaluated at our site during the 05 trial -- did not demonstrate any significant atrial or ventricular arrhythmias at all during the trial.

With regard to sinus mechanism changes, I think if we go back and look, both the systolic and the diastolic blood pressure in the two highest dose groups are also still somewhat reduced at 24 hours, and the most likely explanation for the residual increase in heart rate is still the persistence of some reflex tachycardia on the basis of those reductions.

Not surprisingly, the return to baseline is dependent upon the depth of the blood pressure reduction and, this being a fixed dose trial, we in fact had substantial reductions in blood pressure at the highest doses.

DR. WEBER: One of the questions that the committee is going to consider a little later this morning is the relationship between plasma concentrations of drug and hemodynamic effect. I notice from the data that you presented that the dose of 0.1 was associated with approximately a steady plasma concentration of about 5 nanograms per mil.

Do you have any sense, Dr. Taylor, of where you reach some kind of a therapeutic threshold with this drug? I think later on, when we're debating what might be the most appropriate starting dose, should we work with the suggestion made by Dr. Luther of starting with 0.1, do you have any basis for that in terms of plasma levels?

DR. TAYLOR: Well, there are three components to that answer. The first is that statistically the 0.1 microgram per kilogram per minute dose was the lowest dose that produced a statistically significant effect on the blood pressure, both as assessed by Neurex and by the FDA medical reviewer in the 05 trial.

The dose proportionality is really quite consistent among the 06 trial that Dr. Ellis reported where plasma concentrations are really quite comparable to the 05 trial and some of the comparable

doses in the renal function trial as well. So we're dealing with normal volunteers on one hand who are both salt repleted and salt deplete, and we demonstrate they are quite similar to both mild, moderate, and severe hypertensives.

So although the hemodynamic effects were less noticeable in normal volunteers than they were in hypertensives, the dose proportionality to infusion rate was really quite good related to plasma concentrations.

The second part of the answer relates to the length of time to which people have been exposed to this drug. Clinically, when you look at what happens by 48 hours of continuous infusion, there appears to be some offset of effect. There was never a loss of effect, but there was clearly an offset of effect.

So if you looked at what that plasma concentration might do after the patient had been exposed for 48 hours, you would probably see less of an effect than you would if you evaluated that plasma concentration during initial infusion.

DR. WEBER: Is there any patient or type of patient in whom the generality of these data would not apply? Are there patients in whom I might wish to

start with a lower dose than .1, in whom I might anticipate relatively higher plasma concentrations or, as far as you know, that is not an issue?

DR. TAYLOR: No. We had a couple of patients in whom we abruptly discontinued the drug during the pilot trial. We thought that one of those patients was getting 0.8 micrograms per kilogram per minute, and she in fact was actually getting slightly over 1 microgram per kilogram per minute.

She had very predictable plasma concentrations, but a substantial reduction in blood pressure, and it was on the basis of that patient and one other patient in whom discontinuation had -- discontinuation of the drug was required that we chose the maximum tolerated dose.

The dose proportionality to infusion rate and plasma concentration were maintained in all of those people.

DR. WEBER: Barry, I've got some questions I'd like to ask some of the other presenters, but would you like to finish with Dr. Taylor while he's at the podium?

CHAIRMAN MASSIE: Mike, we might ask Dan if he has any specific questions.

DR. RODEN: I don't think I have any

specific pharmacokinetic questions right now. I have other questions.

CHAIRMAN MASSIE: Well, Mike, why don't you continue to the others.

Well, let me just follow up on Mike's last question, Addison, before you go, since we might be more efficient that.

The question about whether you would ever want to start lower, seems to me to be probably determined by the indication of level of blood pressure. There are two indications that they're talking about. One is severe malignant blood pressure, which presumes that people are going to be starting from a very high level, but the second is just people who you are recommending using this drug as a substitute for oral therapy, who might have quite mild or at most moderate hypertension, for instance.

Would you still think that a .1 dose is the appropriate starting dose?

DR. TAYLOR: I think the absolute levels, Dr. Massie, would depend upon your goal and would depend on the baseline level of blood pressure. The proportionality, though, appears to be reasonably good.

You get far less of an absolute reduction

in blood pressure, for example, in normotensive individuals, and yet proportionate to dose they are about the same. So a ten percent reduction when you start with a systolic of 120 is not the same as when you start with a systolic of 200.

Yes, I would think there are situations in which one might like to achieve a much more modest reduction in blood pressure, and I think Dr. Luther alluded to the possibility of using less, and I think you could use reasonable guidelines to determine what degree of blood pressure reduction you're likely to get.

CHAIRMAN MASSIE: Ray, you had a question?

DR. LIPICKY: Well, two questions, I guess.

DR. LUTHER: Dr. Lipicky, perhaps before your question I'd like to amplify that we have thought carefully about the usual starting dose, and all of the different populations studied with fixed dose infusions leads to the conclusion that the 0.1 microgram per kilogram per minute infusion rate is the one that induces statistically significant and clinically significant reductions in blood pressure.

I would add, with all of the Smith-Kline & French experience where patients were titrated, and

we have patients with a variety of diseases, they came to the same place. The usual dose was between .1 and .3. Occasionally, and very occasionally, the doses were higher or lower.

In addition, we have not presented the data, but the data do exist indicating that the kinetics of the drug are not altered in the presence of hepatic disease or renal dysfunction, which adds an additional level of comfort that there are not subsets of patients who are going to have an extraordinary response based on altered pharmacokinetics.

CHAIRMAN MASSIE: Ray?

DR. LIPICKY: I guess I have two questions. One is: You've described twice that something happened at 1 microgram per kilogram or above, something bad happened, but you didn't describe what happened. Could you do that, please, and how often that happened?

DR. TAYLOR: Well, fortunately, it only happened twice. We started the pilot trial with a dose of 1.6 micrograms per kilogram per minute. The hypotensive effect at that dose is remarkable, and although the patient felt unwell through the first 12 hours of the infusion, we were able to continue with the infusion.

Systolic blood pressures as low as 70 millimeters of mercury, but asymptomatic were achieved with those doses. In retrospect, that patient actually received closer to 1.9 micrograms per kilogram per minute than 1.6, because of some variations in the way the drug was made up by the research pharmacist.

The two patients that had a problem both had an initial prompt reduction in blood pressure and a prompt reflex tachycardia. In both cases, after 30 minutes in one patient and approximately two hours in the second patient, an overriding bradycardia effect was noted, which we think is probably activation of ventricular afferent reflex, a Bezold-Jarish type reflex, with resulting further reductions in blood pressure to values we thought were clinically very unsafe.

The patients were both treated with prompt cessation of infusion, elevation of their legs, and expectant waiting.

DR. LIPICKY: How low did the blood pressure go?

DR. TAYLOR: Oh, 50/30 in one case, and 70/40 in the second case.

DR. LIPICKY: And how did those patients

feel?

DR. TAYLOR: They felt very bad.

DR. LIPICKY: They felt bad?

DR. TAYLOR: They actually felt a bit bad before, but when they became bradycardia, they felt even worse. Fortunately, in both cases there was a very prompt return to blood pressure to levels that were not associated with any significant symptoms, and the patients recovered without incident.

DR. LIPICKY: Okay. You've raised a third question in my mind, which I'll ask now, and then I'll ask the second question after that.

So it could be that beta blockers are a problem? That is, if people are on beta blockers, you would not have the same predictable dose response relationship?

DR. TAYLOR: That's a very good question, and I'm not sure that I can address it. Perhaps the database in the 06 trial where patients were transitioned to oral therapy that included beta blockers and had concurrent administration of fenoldopam would address it.

I think it's a reasonable concern. I suspect that part of the effect of the drug is lost because of the reflex tachycardia, and so one might

expect that there would be a substantially greater hypotensive effect if the heart rate were not allowed to increase.

DR. LIPICKY: Well, it might be worth looking at those patients that had beta blockers concomitantly, but there weren't very many.

DR. TAYLOR: That's correct.

DR. LIPICKY: My second question before that issue -- before that thought came up was: In the severe hypertension trial or malignant hypertension trial, whatever you want to call it, what do you attribute the fall in blood pressure to in the .01 micrograms per kilogram per minute?

DR. TAYLOR: Do you want to answer that?

DR. LUTHER: It is, Dr. Lipicky, impossible to make a definitive attribution as to the hemodynamic response to that particular dose, because there is not a true negative control group in the study. There was not a placebo control.

So the question is the issue is confounded. It could be drug effect. It could be an effective dose or it could be non-drug effect, environmental effects, putting the patient into an emergency department and so on.

There is substantial literature that

suggests that, when you take a severely hypertensive patient off the street, put him at bed rest in a controlled setting, that with no treatment their blood pressure goes down. My bias is that what we are seeing at that dose, which was chosen to be a minimally effective dose based on the Gestalt of the extant titration data, that this is not drug effect, but I can't prove that.

DR. LIPICKY: But indeed you're recommending as a starting dose a dose ten times higher than something that, compared to baseline, looked like it worked pretty good.

DR. LUTHER: In fact, that is true, but the recommendation is strongly based on two other factors. One is the placebo controlled study that Dr. Taylor reported in which the 0.1 dose is the first dose that is, in fact, clinically and statistically significant in lowering blood pressure, and that that is the low end when patients are titrated, and Smith-Kline has a lot of titration data when titrated from very low doses.

The vast majority end up in the range of .1 to .3.

DR. WEBER: As a matter of fact, Ray, if you look at the detailed review of that study, a

number of patients who were first thought to be eligible for entry were drifting down during the final hour before the infusion began. I suspect that this is an environmental effect.

In fact, I was going to ask the same question as you, and make the point that probably what we are seeing with this or possibly what we're seeing with this .01 dose is, in fact, not a drug effect, and if we then would regard this treatment arm as a kind of placebo arm, would it be legitimate to even subtract the effect of this so called dose to see what the other doses are really accomplishing.

DR. LIPICKY: But does that mean that the .03 dose also has no effect?

DR. WEBER: Well, it was just borderline, not quite different from .01, and the absolute number of millimeters of mercury over a period of time was not that dramatic. I could be reasonably well persuaded that, if you put someone to bed, that you would see that kind of downward change in blood pressure.

In fact, I wonder how efficacious the intermediate doses of the drug are. I mean, you could turn this whole question around.

DR. LIPICKY: Well, I mean, certainly, the

dose response relationship must be continuous.

DR. WEBER: Yes.

DR. LIPICKY: And any plasma concentration is going to do something.

DR. WEBER: Yes.

DR. LIPICKY: And there is no threshold effect. You don't have to get to some plasma concentration, then everything happens, and then if the plasma concentration goes higher, nothing more happens or if the plasma concentration is lower, nothing happens. I mean, it's not a threshold effect. Right?

DR. WEBER: Well, that seems to be the case, though --

DR. LIPICKY: So what you're talking about is what you think is a clinically relevant change in blood pressure in 20 minutes or an hour or four hours?

DR. WEBER: Well, at four hours there was a useful fall in blood pressure in that .01 group. The question is was it due to the drug or was it due to something else. I mean, this is always the curse of not having a true placebo.

DR. LIPICKY: Well, what about at .03? Take the .03.

DR. WEBER: Okay.

CHAIRMAN MASSIE: Well, let me just interject something. Between one hour and four hours they were able to raise the dose, and a high proportion of patients did have a dose raise. So at four hours you don't know -- you don't have a stable dose. Only the first hour, as I remember, was a continuous dose, and then what was it, 50-70 percent of people in the .01 went up between one and four hours?

DR. ELLIS: About two-thirds of the patients in the low dose group were maintained at a fixed rate. During the first hour 64 percent of the 0.1 stayed fixed and 87 percent of the high dose group stayed fixed.

MS. STANDAERT: Sorry, sir. Could you give your name, please?

DR. WEBER: Yes, we need the names.

DR. ELLIS: I'm sorry, Dave Ellis.

CHAIRMAN MASSIE: Maybe we should go on with Mike Weber's questions then before we spread too far through the panel.

DR. WEBER: Yes. I'd like to get back, Dr. Ellis, to the issue of no rebound or the claim of no rebound. Do we have any experience from studies of people with really severe hypertension who were not

transitioned to oral drugs?

Now oral drugs will conceal and hide everything, but in my way of looking at the world, if you have a very short acting intravenous drug and you suddenly turn off the spigot, the blood pressure is entitled to zaph up very rapidly, and in some people possibly to overshoot.

Do we really have information that this is not a problem in severe hypertensives?

DR. ELLIS: I think we do. We don't have it from the Neurex experience, but this has been looked at in the SKF experience. They've followed some of their patients for up to 48 hours after the termination of the infusion, have compared the blood pressure during this recovery period with the pre-infusion baseline levels.

In those comparisons, there are relatively few patients that rebound above their baseline. There have been a couple, but it's not been a large percentage. I think our best data comes from Dr. Taylor's study in the mild to moderate. Certainly, in our experience we didn't do the experiment.

DR. LUTHER: Dr. Luther. One additional insight, in that we have a substantial number of patients who have been treated in the perioperative

setting in which the drug is administered for a reasonably short period of time, and we have not experienced a rebound phenomenon there. Pressure comes back to a -- It's hard to know what the baseline is in that setting after a CABG procedure, but blood pressure comes back up promptly and not in a severe manner.

DR. WEBER: Yes, but of course, the people who are treated in the perioperative period tend not to have particularly high blood pressures. They tend to be people with just mildly increased blood pressures whom the anesthesiologist or the surgeon, for whatever reason, would like to have the pressures relatively low; but if the Smith-Kline experience earlier on didn't show that to be a factor, I guess it's not --

The data you showed, Dr. Ellis, indicating that you might need more dose in patients with evidence for renal dysfunction -- do you have any evidence for whether this is a reflection of chronicity? In other words, are people with renal dysfunction who need high doses people who have had hypertension for longer or have had a more difficult or lengthy history? Do you have that background?

DR. ELLIS: We don't have that sort of

medical history in this patient population. I think it's clear that that subgroup of patients we identified, just by dichotomizing according to their creatinine, clearly had a more severe hypertension. Those 18 patients that we sorted out had a mean diastolic at baseline of 146. That's about ten millimeters higher than the rest of the population.

I think, if you want to get into how this group of patients behaves on therapy in general, we can have Dr. Murray Epstein or Dr. Oparil speak to that.

DR. WEBER: I don't think that's necessary. I was just curious in case it might give us some guidance again in selecting patients for this.

Finally, was there any --

DR. MATHUR: Dr. Mathur. I would just like to add that, really, I think the better answer to the question regarding patients with renal deficiency comes from the Shusterman paper that Dr. Ellis presented, because there the baseline blood pressures were equivalent in the patients with the chronic renal insufficiency and those without.

The group with renal insufficiency had a mean clearance of about 39 compared to a mean clearance of about 97 in the non-renally impaired, and

that study was specifically designed to answer that question, and it was a titration to effect study.

Blood pressure was brought down equivalently in both.

CHAIRMAN MASSIE: You need to talk a little bit louder. Sorry.

DR. MATHUR: I'm sorry. It was a titration to effect study. Blood pressure was brought down equally, therefore, in both groups, with very similar dosages, as Dr. Ellis showed. So I think that really helps us to believe that it's unlikely that we're going to overdose these patients with renal insufficiency, in particular, and clearly, some patients with renal insufficiency do have quite severe hypertension that accompanies their renal disease and typically require more and greater doses of antihypertensives; and if this is the case in individuals, the dose can certainly be titrated upwards.

DR. WEBER: There was are quite a large subgroup came in with clonidine allegedly or possibly rebound. Did they respond as well as other patients to treatment?

DE. ELLIS: Yes, they did. We did a subgroup of those 20 patients and dichotomized the

population, and their pharmacological effect was roughly comparable to the other 80 patients. That didn't appear to be an issue.

CHAIRMAN MASSIE: Well, thanks, Mike. I guess it's time to get the rest of the people in. Let's start -- I guess I promised Dan the first crack at it, because of the pharmacology. Then we'll start on that end and go down.

DR. RODEN: Okay. The pharmacokinetics themselves seem pretty --

CHAIRMAN MASSIE: I can't hear too well.

DR. RODEN: The pharmacokinetics themselves seem pretty straightforward, and there's a pretty clear dose proportionality between infusion rate and plasma concentrations achieved, and those aren't -- So that's not -- You offered me the opportunity before, and I don't have any questions but that specifically; but I guess my concern is the actual -- the statement that there is clinically significant efficacy with the 0.1 microgram per kilogram per minute dose.

The statistics are not really dwelled on. The actual change in blood pressure, particularly if you compare it to the .01 mcgs per kilogram per minute dose, is small. I understand why one would want to

focus on that dose, because any higher dose then results in this tachycardiac effect, which presumably is not desirable.

So I want to have a sense from someone about how often it was that people actually needed to go to higher doses than that to control their blood pressure. I didn't -- I was a little confused about the dose titration part of the -- particularly, the severe hypertension trial.

The systolic blood pressure data looked like there was no difference between the .1 and the .3 microgram per kilogram dose. I'd like a comment on that, and the R values that are presented in the written material are -- show a correlation between dose and effect. The correlation has a correlation coefficient of in the .3 range. So that, although statistical significance is achieved, I don't think that that's probably very meaningful.

So those are sort of issues related to where the dose is with respect to where the safety issues might be. I think that the problem may be that you're sort of dealing with a relatively narrow range.

Let me just sort of ask one other question that's related. That is, the problem with heart rate effect is presumably patients with unstable or the

potential for unstable ischemic disease. So I want to know whether those patients were specifically excluded or screened for in the trials, and what other exclusion criteria there were.

CHAIRMAN MASSIE: So maybe the easiest question to answer is the first -- the last one, and then tell us something about this dose range. Are we convinced, if you strike out the .01 "placebo" effect, that .1 works and, as you go up, what happens? But first answer the -- Were unstable patients or people with known coronary disease include?

DR. ELLIS: They were not specifically excluded by the trial. The only cardiovascular exclusion was malignant arrhythmias, and 17 percent of the patients were read by Galen Wagner as having old MIs, and about ten percent of the patients had some reading of ischemic findings at baseline.

CHAIRMAN MASSIE: Did anybody get chest pain during the study?

DR. ELLIS: Several people had worsening of their chest pain. That was one of the entry criteria. There were a few patients that had chest pain as an adverse event.

The two patients that left the trial during the first hour due to adverse events -- one

left for headaches. The other one left for headache plus worsening shortness of breath.

I don't think anybody left because of chest pain.

DR. RODEN: Then the other question was sort of this vague sense of unease about the choice of the .1 as the starting dose, when it doesn't look like there's -- It looks like you would actually have to use a higher dose in at least the malignant hypertension patients, and how that plays into the encroaching on the range of dosages that might be associated with side effects. I don't know how to ask that better.

CHAIRMAN MASSIE: Ray, do you want to answer that question?

DR. LIPICKY; No. i want to just interject a thought, and maybe you will disagree with the thought; but it seems to me that, in the mild hypertension trial where there was a placebo, one can fairly easily detect where the dose response relationship for this drug starts.

So you can then take that information and say, well, malignant hypertension is a different disease, and this dose response relationship no longer applies, or you can say that probably that dose

response relationship still applies, but you want bigger or more prompt reduction in blood pressure. Therefore, you would want to use a higher dose.

Then the other question I would ask would be: What evidence is there that, in fact, in malignant hypertension, you want to bring the blood pressure down fast in big amounts, and whether or not one shouldn't simply look at this from the point of view of when you can up-titrate and to what dose you would up-titrate?

So that you would start at some dose and, if at 30 minutes you didn't have a big enough effect to suit you, you would up-titrate and etcetera, etcetera, and where the maximum limits might be, and whether that might not be a better approach than saying in ten minutes I want to have a 30 millimeter drop in blood pressure.

CHAIRMAN MASSIE: I just wanted to point out something, although I lost the page now. But at least in the sponsor's brochure where they show the dose/time/blood pressure curves, seems fairly apparent that there's an effect at .1. Where was that page?

I think it's page 50. Is that right? The diastolic is at 50, and the systolic is at 54, and it does look like there's at least a -- particularly

focusing at one hour, which is the last point at which we know everybody was on the same dose before they could be titrated.

It did seem like that. So maybe Ray's question is the question. How high can you go, and how do we know how high we can go?

I've been told we have to take a break perhaps after answering that question.

DR. RODEN: And what happens when you go that high?

DR. LUTHER: Dr. Luther. Let me take -- make an attempt to answer how low and how high. I agree with Dr. Lipicky that examination of the pharmacokinetic/pharmacodynamic trial gives a pretty good indication with placebo control of what the dose response curve looks like, and you may recall from the presentation that we showed a comparator -- a comparison slide in which blood pressure reductions and equivalent doses in the mild to moderate and the severe or crisis patients were reasonably similar.

I think that one can draw a reasonable inference from that, especially given that the steady state plasma concentrations were comparable in these different populations.

How high can one go? Clearly, initiating

a dose of 1 microgram per kilo per minute or higher as a constant rate fixed infusion, the starting dose, is unacceptable. It produces, as Dr. Taylor indicated, unacceptable hemodynamic response. However, patients who have been studied in a titration setting can be effectively and safely have the dose driven up to 1 microgram or higher, as needed by the physician.

So the issue is one of there being a graded -- There is a graded response, and one has to find a reasonable starting dose. How low is reasonable? Again, I go back and say that the best data that we have is placebo controlled, and the dose response curves looking at the comparator -- comparing the two trials that we presented, they are qualitatively rather similar.

CHAIRMAN MASSIE: Okay. I think that we need to take a break. I'd like to limit it to about ten minutes, because we do want to get through this this morning. Then we'll come back and finish up with questions.

(Whereupon, the foregoing matter went off the record at 10:50 a.m. and went back on the record at 11:08 a.m.)

CHAIRMAN MASSIE: Okay. We're going to continue with the questions, starting with Lem down

there.

DR. MOYE: Yes. I have one or two technical questions. It's unclear to me in the analysis of the parallel trial looking at four doses just why the stat analysis is called a pairwise comparison. I mean, if I understand this right, the point was to compare patients at the highest dose, the 0.3 dose, to the changes in blood pressure for the patients at the 0.01 dose.

So I'm just not sure what's so pairwise about that? I mean, what's pairwise, I guess, is the change within treatment group, because you have to look at the change in pressure, but that's the only correlation you're dealing with. Is that correct?

DR. LUTHER: The question will be answered by Dr. Francisco, our statistician.

DR. FRANCISCO: It was a two-sample T-test. I think that it's just a semantics difference there.

DR. MOYE: Okay. So it really wasn't pairwise.

Now the primary -- There was one and only one hypothesis test to be carried out per protocol, I see, involving the 01 dose, the 0.01 dose, and the 0.3 dose. Is that correct or was there a plan to also

prospectively look at comparisons between changes in blood pressure for the other doses compared to changes in blood pressure for 01 -- 0.01?

DR. LUTHER: The primary comparison was between the high and the low dose, but it was anticipated that comparisons would be made with the two intermediate doses against the low dose as well.

DR. MOYE: So when it comes down to choosing the most appropriate dose for therapy, is the notion here to, after you've kind of hit on the -- you have significance for the 0.3 and the 0.01 dose, to then look for other winners?

DR. LUTHER: This is Dr. Luther again. I'm not sure I understand the point that you're raising.

DR. MOYE: Well, the point is simply that, when you -- Did you decide prospectively that the 0.1 dose was a potential choice of a dose for the institution of this therapy or was that decision made after you looked at the data?

DR. LUTHER: The 0.1 dose was not prospectively identified as anything but an intermediate dose between the 0.01 and the 0.3. Prospectively, we defined the primary endpoint as a comparison of the -- direct comparison of the two

highest doses on recumbent diastolic blood pressure change from baseline at four hours.

DR. MOYE: Without reporting the standard deviations here, it's difficult to judge the relative equivalence in the blood pressure reducing capability of each of the medications. Is it possible that the reduction achieved by the 0.03 dose is equivalent to the reduction achieved by the 0.1 dose?

DR. LUTHER: We did not test that.

DR. MOYE: So what exactly was your hypothesis testing strategy here?

DR. LUTHER: The hypothesis was to determine whether or not fenoldopam was effective in reducing diastolic blood pressure when given as a fixed rate infusion, and the endpoint was recumbent diastolic blood pressure at four hours, and the comparison was against the surrogate placebo group, mainly the 0.01 dose.

DR. MOYE: Okay, and the rest is pretty much exploratory, just looking to see what's there?

DR. LUTHER: I think Dr. Lipicky wishes to comment.

CHAIRMAN MASSIE: I think we're bogging down. I suspect what you're saying is: Is .05 the right threshold, because there were implicit multiple

comparisons being made here?

DR. MOYE: I was eventually headed there.

CHAIRMAN MASSIE: Yes, and I wanted to move there more rapidly.

DR. MOYE: Okay.

CHAIRMAN MASSIE: But it does look like it's a .018 for the .01 -- I mean for the .1 dose level. Does that discourage you from thinking that that does work?

DR. MOYE: Well, I'm just pondering what the advantage -- what the relative disadvantage is of not having a prospective plan in deciding how you're going to determine the most efficacious dose, given you're looking at more than two of them, versus just seeing what the data show you.

The difficulty I have with the latter -- I understand why they did what they did. The difficult I have with the latter approach -- and this is not a lethal difficulty, but a difficulty I have, nevertheless -- is that different datasets might lead to small differences in the changes in blood pressure over time, and would lead to another decision, a different decision, for the optimal dose to be used here.

CHAIRMAN MASSIE: Ray?

DR. LIPICKY: Well, this is similar to the comment I made before, and I'd like to just lay out a broader spectrum of background.

The question here, it seems to me, is: Is fenoldopam different from placebo in that, if you can say yes to that, then it is an antihypertensive agent. Then the next question is -- and without making a judgment as to whether or not the answer to that question is yes or no -- If the answer is yes, it does have antihypertensive effects, then the other question seems to me to be: Is that effect related to dose, and over what dose ranges is this not placebo?

That's a descriptive problem. That is not a hypothesis testing problem. Then if there is some range of doses in which this is not placebo, since we're only dealing with the blood pressure lowering effect and there are no event data in terms of efficacy, it's going to necessarily be physician's judgment as to how quickly or how largely they want to lower the blood pressure.

So then the next question is: If you start at some rate, how long do you have to wait before you can increase the rate of infusion in order to get to the next level that you want to get to. So that that's a descriptive problem, and it's not a

hypothesis testing statistical problem.

The hypothesis -- The only hypothesis testing part is: Is this an antihypertensive agent? The rest of it is: How does its effect relate to blood pressure, and how can clinicians use it without getting a bigger effect than they want or a faster effect than they want, and whether or not there is enough information possible to write that set of instructions for use.

CHAIRMAN MASSIE: And let me just interject, because we have something we have to do today, which is to answer some of those questions; but we may not -- This committee may not be in the position to best evaluate the data to answer all those questions. Is it true that you would just like us to (A) decide whether it's antihypertensive; (b) decide whether the data themselves are sufficient for the agency to --

DR. LIPICKY: That is how the questions read.

CHAIRMAN MASSIE: Right. And not necessarily --

DR. LIPICKY: If you answer the questions, that's --

CHAIRMAN MASSIE: -- all agree here that

we can pick out the dose and the interval?

DR. LIPICKY: Well, I don't see how you have the ability to pick out a dose, because you have no idea what blood pressure level you need. Okay?

CHAIRMAN MASSIE: All right. I think I understand.

DR. LIPICKY: And all you know is that this is an antihypertensive. Maybe you know that. Maybe you will say yes to that.

CHAIRMAN MASSIE: Okay, good. Let's keep on going.

DR. LIPICKY: And that -- Then the next questions are whether operantly a set of instructions for use can be written, and in what patient population you know that that's true for, and that's sort of how the questions lay out.

CHAIRMAN MASSIE: I know. Okay. Moving down, JoAnn?

DR. LINDENFELD: I have just a couple of questions. One is: I don't see. Was there any systematic look for infarcts in patients treated with hypertensive emergencies or were infarcts just at the discretion of the clinician? In other words, were there routine EKGs or enzymes or any routine review of the charts on any of these patients?

DR. ELLIS: This is the treatment. Electrocardiograms were repeated at six hour intervals.

DR. LINDENFELD: Any enzyme determinations at all?

DR. ELLIS: I'm sorry. I didn't hear the question.

DR. LINDENFELD: Any cardiac enzyme determinations?

DR. ELLIS: No, they were not routinely done.

DR. LINDENFELD: Then another question I have is: Generally, drugs that cause a reflex tachycardia are considered to be contraindicated in LB failure or acute ischemia, perhaps -- certainly in dissection. There's nothing in the precautions or the warnings about that with this drug. I wonder if you could comment on that.

DR. ELLIS: I'm sorry. I didn't hear the question.

DR. LINDENFELD: Sorry. Generally, in recent reviews of the treatment of hypertension, drugs which cause reflex tachycardia are considered to be contraindicated in ischemia, LB failure or dissection. I notice that in the labeling you've proposed, none of

the warnings or precautions mention that. This drug certainly causes a reflex tachycardia.

DR. ELLIS: Yes. that's true. At the .1 dose that we're choosing or recommending, the mean increase at four hours was four beats per minute.

DR. LINDENFELD: That's a recommended starting dose. I think there's a wider range, and certainly tachycardia occurs at all doses. It was minimal at .1.

DR. ELLIS: That's correct. One of the things that we did to address this is to look at the double product in these patients, to see whether this really was an issue, whether increasing worked in these patients, and in all our dose groups the double product went down.

DR. LINDENFELD: Well, that's true, though, also of other drugs that lower blood pressure, but there is still hydralazine diazoxide, but they're still considered relatively contraindicated in those situations, even though they lower double product.

CHAIRMAN MASSIE: Okay. Rob?

DR. CALIFF: I have just a couple of things. First, just a plea in data presentations to clearly identify whether you're showing in error bars standard error or the mean, the standard deviation or

the confidence intervals. It particularly bothered me where you wanted to show another difference. We saw 95 percent confidence intervals, but where you wanted to show a difference, I think it was standard error of the mean, which visually -- display can be very confusing if you're trying to understand what the data mean.

Fortunately, we can go back to the books and figure it out, but just a plea, when presentations are made, to make our job easier.

The second question is -- the second issue, just to follow up on the previous question: Adverse events, I think, can be very confusing in trying to understand what they mean. I'm presuming that all the adverse events you showed included no "yes or no" check boxes, but were all sort of fill-in-the-blank if something bad happened.

DR. ELLIS: That's correct. The adverse event forms, at least in our trial, were just a piece of paper. You described the adverse event and when, what, where, why, how.

DR. CALIFF: You said you got EKGs. Were they systematically read specifically to see if there was evidence of myocardial infarction or new Q waves?

DR. ELLIS: That's correct. Galen Wagner

read all of our electrocardiograms for this trial centrally.

DR. CALIFF: But there was a specific question to -- I know him pretty well. He's right down the hall from me. There's a specific question, new Q wave, yes or no?

DR. ELLIS: He used the same case report form for his reading that he's used in some of the myocardial infarction trials. So he was very attentive to that, yes.

DR. CALIFF: Then you showed possibly or probable drug related adverse events. How would an investigator know whether, if a patient had chest pain, it was drug related? Is there any utility in doing that, rather than just reporting all adverse events that occur?

DR. ELLIS: I think in our adverse listing for just the general adverse events, it was all adverse events that we've reported. We've not sorted our own into causality.

The serious adverse events that were reported -- those were the ones that were regarded by the investigator as related or probably related.

DR. CALIFF: Were there other serious adverse events that were not said to be drug related,

and how would an investigator know that an adverse event wasn't drug related?

DR. ELLIS: It's always a judgment call. In our own case, the events -- there were no serious adverse events that were not considered related. With regard to the SKF experience, it's hard to answer that question.

DR. CALIFF: So there weren't any that fell in that other category in your studies?

DR. ELLIS: No.

DR. CALIFF: Good. The last thing, just to clarify, because I think the only concern I have is this reflex tachycardia and what may be going on with the heart in the absence of systematic looking for myocardial ischemic events.

Seems like this receptor or its analogous receptors -- do they exist in the heart and, if so, what do they do?

DR. TAYLOR: That has not been well studied. We actually have some ongoing studies right now looking at both the muscle and the endocardial surface of the human heart, and we're not really prepared to answer that question; but we will be looking for both the D1 and the D2 receptor family.

The D4 receptor has been identified in the

human heart by Dr. Carey's group, and they're the people who are working with us to do this further identification. So we can't really answer the question.

DR. CALIFF: Thank you. I look forward to seeing it.

CHAIRMAN MASSIE: Before Marv goes on, I just -- because this may take a little preparation on your part. You show adverse effects, and Rob has homed in on a little bit of that, and your statement was these are not unexpected in this population.

Since there's not a lot of placebo data, it makes it hard to evaluate whether -- unexpected or not, whether they're more frequent. It seems reasonable, if anybody has the data to compare, since the .01 is an implicit placebo, .03, you think, is below the effective dose -- to compare the side effects, adverse effects on .1 plus .3 to .01 and versus .03.

I just want to know if there's a dose related side effect incidence, because we don't have a placebo effect, and maybe you might need to pull that out while we go on and have Marv ask some other questions.

DR. KONSTAM: Okay. My questions, I

think, follow along with Dr. Califf's, and they reflect substantially to the tachycardia.

You referred to it as reflex tachycardia. How do we know that there is not a direct chronotropic effect of the drug?

DR. LUTHER: In the preclinical pharmacology studies there was chronotropic identified.

DR. KONSTAM: Okay, and there are no -- There are no data from the human experience that we can draw on to tell us about this, one way or the other?

DR. LUTHER: This is Dr. Luther again. I think that the best evidence is that, when this drug is administered, it clearly interacts with the receptors. One can see that occurring in the kidney at doses below which there is a vascular response, and the only time that we see a cardiac chronotropic response is in the presence of significant hypotensive effect.

So that one cannot exclude a direct effect, but the fact that one is not seeing it at lower doses --

DR. KONSTAM: Okay. I'm not convinced from that, but maybe it doesn't matter, but I just

wonder about calling it, you know, reflex tachycardia without any way of knowing a little bit more clearly that there is or is not some direct cardiac effect; but I'm not sure whether that matters or not.

I'm more concerned about the potential clinical impact, and I guess I have a couple of comments, and maybe you could reflect on them.

I'd like to see, and this relates to the question about adverse effects -- I'd like to see some kind of more detailed systematic investigation of the potential presence of adverse ischemic events in the population. I'm not sure how to conduct that, but you have a population of patients in which you say that there is a presence of patients with underlying ischemic heart disease, and nothing seems to have jumped out at us from the dataset that exists; but this is a specific important concern in a population of patients that are hypertensive, many of whom are likely to have ischemic heart disease.

I guess you'd like language that is at least permissive of patients who have unstable ischemic syndromes, and I don't feel that there is enough of a systematic look at the potential for stimulating ischemic events in your populations. I don't know if you want to comment on that.

DR. LUTHER; I think the only comment that I can make is that we have not conducted a prospective study in patients with known coronary disease, and with the appropriate controls to be able to answer that question definitively. What we do have is the extant database in which there is not a signal, a strong signal, of --

DR. KONSTAM: I'm not sure I'm asking for another study, but I would -- I'd like, you know, maybe not -- Maybe we don't need an instant answer, but I guess I would like to say to the agency that I'd like to see some discussion of scrutinizing the existing database a little bit more proactively to look for evidence of that. I'll just leave it with you.

CHAIRMAN MASSIE: Ray.

DR. LIPICKY: I'm not sure. Maybe you could help me clarify what you're saying.

For most agents that I know that have been studied in malignant hypertension, -- diazoxide, Labetolol, nitroprusside -- when those agents lower blood pressure, there are T-wave changes, and there are innumerable reports with a variety of agents of really bad things happening, like optic nerve infarcts and so on and so forth, that are associated with the

treatment of hypertension that is severe or emergent or what have you.

Are you trying to dissect whether or not a direct effect on the heart of fenoldopam is here or whether lowering the blood pressure of patients who have emergent hypertension is not a good thing? What are you trying to figure out?

DR. KONSTAM: I'm just wondering about the labeling wording, and I'm wondering about what types of warnings might ben issued vis a vis the use of this drug in agents -- in patients who have underlying ischemic heart disease or active ischemic syndromes, and I don't see anything that's been presented or written up to really help me too much about that.

Now if you're satisfied about --

DR. LIPICKY: That is correct, but you aren't thinking in terms of there being a direct myocardial effect of the drug that is not described that would --

DR. KONSTAM: No, that was a lead-in question, because I was wondering about that. I don't see -- They are two separate questions.

DR. LIPICKY: Because we do -- and I just want to pursue it for a second, because I must say that, if I'm asking the question of does the drug have

chronotropic effects, I'm fairly comfortable answering that question from having isolated hearts hung in Langendorf setups, which is the most direct way I know of of asking that question.

I'm not sure I know how to do that in the human.

DR. KONSTAM: No, I'd like to separate them as two separate questions. My first question was from my perspective more theoretical, and in terms of use of the terminology reflects tachycardia.

DR. LIPICKY: Right.

DR. KONSTAM: How sure are we of that. I think the more important issue is the clinical use and what the labeling will say about using this agent in patients with ischemic --

DR. LIPICKY: Well, what other labeling has said, for the sake of that conversation, is that you don't know how fast or how much to reduce blood pressure in emergent situations. Go as slow as you can or you think you can, but we don't know how to specify that.

CHAIRMAN MASSIE: Ray, I think, though, that what several people are raising are a little different question than how fast to lower the blood pressure, but whether you can lower it without -- both

in unanticipated and unfortunate tachycardia.

If you go back to -- For instance, we've had this discussion of nifedipine. They keep on saying nifedipine is not indicated for hypertensive emergencies. It's bad, because it causes tachycardia in fact. It causes uncontrolled blood pressure drops.

I think that there are a lot of blood pressure agents approved. We've named a few, diazoxide, hydralazine, nitroprusside, and I think JoAnn was absolutely right. Guidelines being written now say that these agents are not the agents of choice in people who have or are thought to be at risk of having underlying ischemic heart disease, but rather you would like to lower blood pressure with a drug that doesn't raise tachycardia.

DR. LIPICKY: But on what basis are those guidelines based? I mean --

CHAIRMAN MASSIE: Anecdotal evidence that people infarct.

DR. LIPICKY: Yes. I mean, there's -- That's true.

CHAIRMAN MASSIE: And I think that's why people are asking for a systematic look at what evidence of ischemia or what numbers of patients at risk for ischemia have been studied in this context,

because that would be where you would begin to pick up the anecdotal evidence.

I'm a little uncomfortable, having heard that there are five people with T-waves. Now if they all occurred with the same blood pressure drop and the same change in heart rate, I'd be reassured. If they occur at low dose -- only at the high doses and only in the people who got tachycardia independent of the blood pressure drop, then we have to think that maybe what we're precipitating is ischemia, that type of look at it.

DR. LIPICKY: And I recognize that what I'm about to say is inadequate, because the trial was small.

CHAIRMAN MASSIE: Right.

DR. LIPICKY: But there was a nitroprusside positive control, and there was T-wave inversion in nitroprusside as well as with this drug. Now it was inadequate in the sense of there is no event data here. So that the trials are not large enough to determine whether, in fact, there is a net gain.

DR. LINDENFELD; Well, more than that, I believe 80 percent of the patients in the severe hypertension trial had LVH, and trying to interpret

STT wave changes in the presence of LVHs is not going to be a very productive endeavor. So that's why I think the absence of enzymes is a bit of a problem.

DR. KONSTAM: Quick. Well, I just wanted -- I mean to follow up again. Then the concern I have is what do you do about beta blockers, and this was touched on earlier, but I think it needs to be dealt with a little bit more directly.

You know, I think that my impression is going to be that clinicians are going to use this drug in combination with beta blockers, I suspect, widely. I think they are going to be concerned about the reflex tachycardia, and I think that beta blockers will be used.

So I'm concerned about the fact that we don't know too much about the combination of this drug and beta blockers, and what are we going to do about that?

DR. ELLIS: I think there's two sources of evidence. There have been animal studies that Smith-Kline has done together with propranolol, and they've also done a healthy volunteer study looking at propranolol. There the interaction was not particularly great.

It's interesting that it didn't seem to

reduce the reflex tachycardia very much. There was a slight increase in the reduction in systolic, but not much of a change in diastolic. It wasn't a pronounced interaction.

In terms of what happens with patients with severe malignant hypertension, there's clearly no organized studies, and all we have are the observational studies of patients came into and went out with.

DR. KONSTAM: I have one more specific question. Do we know what this drug does to action potential duration in any model?

DR. ELLIS: No.

CHAIRMAN MASSIE: Well, I know Ray thinks my question is not -- will not get an adequate answer, but have you come up with any information on side effects and whether they are more common in the two higher doses? That is, your recommended starting dose and the doses that they are likely to be titrated up to from there?

DR. ELLIS: Yes, we have. We've certainly looked at the overall incidence of adverse reactions versus dose in our study, and it's essentially not related. I can read it to you. We never made a back-up.

CHAIRMAN MASSIE: Sure, why not.

DR. ELLIS: But for the .01 group there were 14 patients with any adverse event. For .03, 13 patients had adverse events. For the .1, 11 patients had adverse events, and for the .3 11 patients had adverse events.

In terms of T-wave inversions, there weren't that many of them called, but the four that were called were in the .01 and .03 group.

CHAIRMAN MASSIE: And I can't remember whether, amongst the serious ones, there really wasn't anything we can pin our hat on as being that serious. Right? Because there were no infarctions, no worsening chest pain?

DR. ELLIS: In our population, that's true.

CHAIRMAN MASSIE: How many patients do you have that have beta blocker background in any of the studies, Smith-Kline or otherwise, and/or got -- didn't look like hardly anybody got beta blockers that run into oral therapy either.

DR. ELLIS: Yes. On the exit -- there were a fair number of patients that came in --

CHAIRMAN MASSIE: No, I don't think -- because they had to be withdrawn. Right? When they

came in?

DR. ELLIS: Yeah. Well, half the patients weren't on anything.

CHAIRMAN MASSIE: Right. No, I don't mean what they came in. How many spent some time on both drugs?

DR. ELLIS: Certainly, in the population that was transferred, there are only a couple that got transferred onto beta blockers. The patients that came into the trial, the 50 percent of the population that did come in, there certainly were more --

CHAIRMAN MASSIE: No, that won't help. I mean, I'd like most of the committee to feel like, if you're going to give this drug to the type of effects we see, then it might not be a good practice to do without a beta blocker on board, and I'm trying to look for some data on that.

DR. LUTHER: This is Dr. Luther. We have -- From the two trials that we have done, because patients were by and large washed out, we have very little drug interaction information. It's essentially nil by design. However, I would call the committee's attention to the fact that there is an extraordinary database with oral fenoldopam in which the drug is given long term in combination with everything,

including beta blockers.

There have been no significant drug interactions identified in that database. We're not here to discuss that database today. So I don't have any data that I can show you.

CHAIRMAN MASSIE: But the agency has that data?

DR. LIPICKY: Yes, but I'm not sure it's applicable, because it doesn't lower blood pressure much under those circumstances.

DR. LINDENFELD: Isn't there a tachyphylaxis to the oral form? So it doesn't tell you much.

CHAIRMAN MASSIE: And the last point I have is that I know there's -- With ibopamine at least, which I guess shares some of the pharmacological activity, there is a tachycardia even in people whose blood pressure doesn't go down -- in heart failure, that is. There's a fair amount of experience with fenoldopam IV and heart failure as well. What happens to the heart rate in those patients?

DR. ELLIS: The heart rate doesn't go up very much in the heart failure patients.

CHAIRMAN MASSIE: What is that? What is

by very much?

DR. ELLIS: Like five beats per minute on average.

CHAIRMAN MASSIE: On the average? That is, I guess, the definition of a tachycardiac response in heart failure. if they go up five beats per minute, in general, they're not ones that end up with good outcomes.

DR. ELLIS: These are the acute intravenous studies that lasted for --

CHAIRMAN MASSIE: So that would not presumably be -- Would the blood pressure go down and up to stimulate a reflex tachycardia in those patients, or was this five beats per minute of intrinsic heart rate increase?

DR. ELLIS: The cases that I've seen -- we've not reviewed this or not prepared to present it in any great detail. The rate looked fairly constant during the maintenance infusion, and they did the same dosing regimen that they used in hypertension, titration to effect. They started at .1 and go up to .3 or .4, look at cardiac output, and then down-titrate and stop.

CHAIRMAN MASSIE: I guess we had better move down the line. Cindy?

DR. ELLIS: You asked if the blood pressure went down in those patients very much. Not very much.

CHAIRMAN MASSIE: So, you know, that plus the ibopamine experience and, as I remember, I guess, would suggest that what we have is an agent that does have an intrinsic tachycardiac effect.

DR. ELLIS: I don't think ibopamine is a fair comparison, because that is really a dopamine prodrug. So I think that compound also has probably some beta effect, whereas it's clear that this drug does not have a beta effect.

I think the best answer to Dr. Konstam's question of whether this was a reflex tachycardia or a chronotropic effect is just looking at the time course in our population. After a peak blood pressure -- or peak heart rate increase about two to four hours, you see a dissipation of that reflex, and by 12 hours the patients are back down towards baseline.

DR. KONSTAM: Yeah. Let me be clear. I asked that question, you know, just for my own information and for semantics, and in terms of how the words are used; but the much more important concern is just the fact that patients get tachycardiac on this drug, and what do we do with that in terms of recommendations and warnings, and what do we do with

the use of beta blockers that are going to be used.

CHAIRMAN MASSIE: Cindy?

DR. GRINES: I see a lot of information about the heart rate compared to nifedipine. How did it compare to Nipride?

DR. ELLIS: They were identical. The hemodynamics of the two drugs in the two studies that SKF reported were very comparable. They both used an up-titration scheme and went to a common target. On average it was about 30 millimeters drop, and the blood pressure reduction was identical by design.

The increase in heart rate was roughly comparable. The Nipride group was a couple of beats per minute less in some cases, but still on the same order of magnitude, 8-10 beats per minute rise.

DR. GRINES: Are there any other trials that are ongoing?

DR. ELLIS: No, there are no ongoing trials either at Centex or SKF -- I'm sorry, Neurex.

DR. GRINES: That's all.

CHAIRMAN MASSIE: John?

DR. DiMARCO: I don't have any questions.

DR. THADANI: A couple of clarifications and questions. In the hypertensive axillary hypertension, was it by design that 49 percent of the

patients were not on any drug for seven days? Does that mean you withdrew the drugs or these patients were noncompliant or was it for the sake of the study you stopped the drug so they could qualify?

DR. LUTHER: No. In the -- This is Dr. Luther. In the malignant hypertension study those patients presented having been noncompliers with their out-patient --

DR. THADANI: Okay. So they were noncompliant not for the study.

DR. LUTHER: That's correct. We did not withdraw anybody from their medication to give them accelerated hypertension.

DR. THADANI: Now another question: One of the concerns always is going to be the tachycardia, but I'm having problems in the hypertensive emergency situation. In the pharmacokinetic database I think those responses on tachycardia go in the right direction, but in the hypertensive crisis, if you want to call that, the tachycardia on the highest dose is really out of proportion to the drop in systolic blood pressure, because a drop in systolic blood pressure is really same at .1 and .3, and yet the heart rate is increased by 20 beats.

So one has to give some explanations.

Something is going on. I don't know what. Do you want to make any comments on that? You could look at page 52 -- no, sorry, 54, systolic blood pressure, and they are really on line. The drop in pressure at .1, .3, I don't think I can differentiate by eyeballing it, and yet the heart rate just stands out. So something is funny there.

So you could argue perhaps that -- I realize the animal model doesn't show you chronotropic effects. The question is, is there something going on at a higher dose, somehow some receptors are getting stimulated, whether it's epinephrine driven, norepinephrine. Something is gong on, and I really feel uncomfortable.

The question is, if I go to .3 -- say, if I go to .5, am I going to see a 50 beat increase in heart rate, and I have no data on that. I realize you are saying that one could be harmful, for whatever reason, a drop in pressure in this. Do you want to comment a bit more on that?

DR. ELLIS: We've asked ourselves the same question. One of the things that we noticed right away when we analyzed the data with the systolic, that it looks like there's not a great difference between the .3 and .1 group, and we asked the same question

you did. Why is that?

Our take on it is that the reflex tachycardia was more related to the drop in diastolic blood pressure rather than drop in systolic blood pressure.

DR. THADANI: But that's a new concept. So I'm not aware of that. Usually, the systolic one is the one that goes. If you are saying you're opening a new, you know, hypothesis, which I don't think is proven in any of the studies -- So we don't know. The question is: Is it a concern and, if I want to go to .5, would I be really worried in patients, CHD patients or whatever? I think one has to explore that.

The third issue: I'm really not sure. The beta blocker issue came in. Sometime beta blocker is useful, sometimes harmful, but especially for tachycardia. The blood pressure doesn't go down too much. I could block the heart rate; I'll feel happy, but in patients, say, at 1 milligram dose, are you saying the blood pressure is down to 50, and then they are actually -- they're in tachycardia. They got bradycardia.

You see it with nitroglycerin, too. It's not unique for this, and whatever receptors are

stimulated. In that situation, if a beta blocker, you could be worse off, because you don't have a compensatory response to increase your heart rate. Pressure is 50. There is no coronary profusion.

So I'm not sure, you know, the database will tell you one way or another. So people have raised the issue, you would like to see the beta block here. I think the patient responses are so different in pressure drop.

So my question to you is the patients who really dropped their pressure. I know the t-half is only a few minutes, but the pharmacodynamic data -- I did not see how rapidly the pressure comes up. I know if I turn off nitroprusside, it goes up very quickly.

Is there a difference that it will take half an hour, two hours for the blood pressure to creep up with respect to the plasma concentration, because I do not see any data?

DR. TAYLOR: If you are asking about the two patients in the pilot --

DR. THADANI: Yes. How quickly the pressure came up or you have to give them suppressors or what happened?

DR. TAYLOR: Both of those patients had systolic blood pressures less than 70 millimeters of

mercury at the time the infusion was discontinued, and within five minutes the blood pressure in both of those people was over 100 millimeters of mercury systolic.

So it came back really fairly rapidly.

DR. THADANI: What about the overall group data and the hypertensive -- When you start the infusion, I suppose you did not stop it, and the pharmacokinetic database, when you stop the infusion, t-half is short. Does the pharmacodynamic parallel it or is the effect maintained for a while?

DR. TAYLOR: There were -- Of the two trials, the only two patients in whom we had to stop the drug were those two people in the pilot study only, and having limited the maximum dose that was infused during the blinded trial, we actually didn't experience that problem. So we never did stop the infusion.

DR. THADANI: But you did stop at 48 hours after the infusion.

DR. TAYLOR: We did stop at 48 hours.

DR. THADANI: So how quickly the blood pressure comes back to normal?

DR. TAYLOR: The blood pressure comes back pretty much as I showed. At the two highest doses,

even at 24 hours, there is still some modest reduction --

DR. THADANI: No, no, but within the first five, ten, 15, 20, half an hour. I know you showed the 24 hour data. What happens in the first 15 minutes, 20 minutes, because you took the pressures every 15 minutes.

DR. TAYLOR: That's correct. We --

DR. THADANI: Does it come back to normal within 15 minutes, 20 minutes?

DR. TAYLOR: No, it doesn't. The longer it's been down, the longer it takes for it to come back.

DR. THADANI: So there's a dissociation between the pharmacokinetic, pharmacodynamic, because the plasma concentration really comes steeply down, and the pharmacodynamic effects are maintained. You know, I'm not criticizing you. This is true with a lot of blood pressure lowering drugs.

DR. TAYLOR: Right.

DR. THADANI: But in an urgent situation, if the pressure really goes down, the patient is having trouble. So you might have to worry about a drug -- blood pressure effect to revert to normal after a long time.

DR. TAYLOR: Well, I think that's a very valid concern, and my response to that is, when we had to discontinue the drug after relatively short exposure times, the return to the baseline blood pressure is fairly rapid.

When you've exposed the patient for a longer period of time and apparently had some compensatory mechanisms called into play by keeping the blood pressure down that way, it stays down for a longer period of time, which is equivalent, as you say, in many antihypertensive trials.

DR. THADANI: My last question is: Ray raised the issue, perhaps the physician could keep on increasing the dose at which level he thinks comfortable. I think, when I look at the data, I'm not comfortable to increase the dose every half an hour. From both your pharmacokinetic database on your page 22 of the red folder given to me by the FDA and on looking at page 54 on systolic blood pressure, the peak effect is almost at three or four hours.

So I feel very uncomfortable to keep on pumping the dose every half an hour, because I have no idea what the pressure is going to do. If I go from .1 to .3 to .5, I might be down by 70 points.

You know, the half an hour data, it looks

only by some, but by four hours. It could be diurnal or whatever in there, but I think it's a bit disconcerting that I cannot, from the database -- I realize we have used the judgment in the past to go slowly, but here slow means four hours or three hours. I'd like some comments from you.

CHAIRMAN MASSIE: And very quickly. We're running out of time.

DR. THADANI: That was my last question.

CHAIRMAN MASSIE: Do you have an answer to time course of increase of dose, and why you picked 30 minutes?

DR. LUTHER: In 30 seconds I can perhaps give a lucid response.

The blood pressure goes down rapidly, and the majority of the effect is seen within the first five or six half-lives of the drug, but the pressure does continue to drift downward. Whether it's drug effect or environmental, it's not easy to sort out those confounding factors.

Our recommendation is for a minimum interval of 30 minutes, based upon the pharmacodynamics; and if one were to start at a dose that's ineffective, I would not -- I would not want to see a patient that I've decided needs parental therapy

to wait four hours to see what I'm going to get. I think that a shorter interval is appropriate, based on the clinical response.

DR. THADANI: Sorry to stop, but every dose is effective. We don't have a placebo, but if I look at even .01, the trend is going drifting down. So I don't know whether you can say --

CHAIRMAN MASSIE: Okay, Ray?

DR. LIPICKY: I thought that you showed a slide of what happened to blood pressure at the end of the 48 hours of continuous infusion, and I don't remember its looking the way you described it. Could you just show that slide again? This is the time course. The x axis is time?

DR. TAYLOR: Yes.

DR. LIPICKY: I want to see the time course, the time course of blood pressure when things are discontinued.

DR. TAYLOR: The only time course we have, Dr. Lipicky, is for the 0.8. This at least compares all the doses four hours after discontinuation and 24 hours after discontinuation for each of the doses that were used in the blinded trial.

DR. LIPICKY: This is the effect, not the going away of the effect.

DR. TAYLOR: Well, the 52 hours, four hours after stopping, and the 72 hour is 24 hours after stopping.

DR. LIPICKY: Okay.

CHAIRMAN MASSIE: I think what we're seeing here that's confounding it is, if you put somebody in bed for 24 hours and control all sorts of things, their blood pressure is not likely ever to come back to the way it was when they got into the trial. This is what we see with hypertension.

So how far they've come back to where they're going to go is a much trickier question.

DR. LIPICKY: Okay, but I'm left with the impression that the time course of disappearance of the plasma concentration of drug is in minutes, and that the time course of disappearance of the blood pressure effect is hours. Is that, in fact, correct?

CHAIRMAN MASSIE: I guess this is the slide you really wanted, Ray. Turn it around. At discontinuation, obviously, the blood pressure -- There's a bump up pretty quickly, minutes, and then there's a further rise that's slower.

DR. LIPICKY: And there is something else, but there is a very rapid change.

DR. TAYLOR: That is correct.

DR. LIPICKY: And then there's something that needs explanation maybe.

DR. TAYLOR: Well, and of course, then we also have the time factor confounded by circadian variation, which is actually maintained. So the longer out you go, the more effect of circadian variation you see.

DR. LIPICKY: And you do not have a slide showing that blown up at the time of discontinuation so you could get a feeling for how fast that is?

DR. TAYLOR: That's correct. The first time point that was plotted was four hours after discontinuation.

CHAIRMAN MASSIE: Okay. I think we've got all the data we're likely to get. I've asked the reviewers whether they want to give us any other view of data, and they think that they don't right now; but if you have any comments as we try to go through the questions, please do kick in.

So we're going to try to get done before a break. In light of that, I'm not going to read this long preamble, which I guess the committee has all had ample opportunity to look at, and move into the actual questions.

The first question is: In the 0.05 study,

the pharmacokinetics study, enrolled patients with mild to severe hypertension, excluding those with any signs of ongoing end organ damage that defines hypertensive crises, these patients received placebo or fenoldopam infused at rates of .04 to .8 micrograms per kilogram per minute.

Our questions, which Dr. Weber is going to lead us in, is: Did the study identify a minimal effective infusion rate for an antihypertensive response?

DR. LIPICKY: Before you answer, Mike, that is not clinically significant. It is an antihypertensive responses.

DR. WEBER: Well, in that case, you made it a little easier, Ray, because I believe the study showed that the .04 dose was different from placebo at one hour. We're looking at a fall in diastolic pressure of 8.2 compared with 2.4. So I assume that's different and, therefore, .04 is an antihypertensive type of dose. .04 is an antihypertensive dose. Similar data apply to the systolic pressure.

So I think the study did identify a minimum effective infusion rate for an antihypertensive response. You could argue, I suppose, that if this was different, there might have

been something between zero and .04 that could have also have a similar effect, but we don't have that.

DR. LIPICKY: Well, just to drag you out a second, and I apologize, so why do you -- What is the data -- Could you just cite the data that says that doses below .4 don't lower blood pressure?

DR. WEBER: No, I have no evidence. That's the point I was making. Maybe if they had tried .02, we might have also had something that looked different from placebo.

DR. LIPICKY: .04? Oh, I see. You said .04 lowers blood pressure.

DR. WEBER: Yes.

DR. LIPICKY: Okay, fine.

DR. WEBER: The second part of the question: If so, to what populations should this finding be expected to apply?

Of course, we don't know from this study. We only know from this study about mild to moderate hypertensives, but having had the advantage of seeing the other data, it seems as though this information applies to patients with all degrees of severity of hypertension.

CHAIRMAN MASSIE: Let's move on to 1(b): Did it identify a maximal infusion rate above which

the effect was unsafe or intolerable?

DR. WEBER: Well, what it did do, Barry, is it identified -- at least this study did -- a plateauing of effect, which surprised me a little in view of some of the other data we had heard; but you can see that 0.4 and 0.8 have very, very similar effects on diastolic pressure and on systolic pressure.

So one could not justify going above .4, at least as far as this study is concerned, for efficacy purposes, but it's interesting that, even though they have virtually identical blood pressure effects, the heart rate does tend to go up a little bit more -- in fact, you could argue, more than a little bit more -- with a .8 dose than with a .4 dose.

So I would be very encouraged to believe that .4, for practical purposes, would be -- based on this study and this experience -- where I would draw my line.

CHAIRMAN MASSIE: Do you think that further rise in heart rate makes it potentially unsafe?

DR. WEBER: Well, it makes -- It's the old story. You're getting a fairly marked further increase in heart rate for no additional blood

pressure effect. So it's all risk and no benefit in this population under these circumstances.

DR. LIPICKY: I want to make just one comment, I suppose. That is, when you see that over a 20-fold dose range there is a continuous increase blood pressure -- or continuous increase in effect, how can you conclude that a change of dose by a factor of two is giving you the permission to say the dose response is flattening there?

DR. WEBER: Well, you know, Ray, it's not -- I agree with what you're saying, and it would be very useful if we had a 1.6 just to confirm that impression.

DR. LIPICKY: Right, and they do. What did that find? That people didn't feel well when their systolic pressure was 50.

DR. WEBER: That's correct. There was profound hypotension, at least that one patient.

CHAIRMAN MASSIE: Which followed tachycardia, which looks like is already there at .8. I guess you've identified a dose above at which, at least for this population -- You think this is population specific?

DR. WEBER: I doubt it, but I'd be a little cautious when it comes to the side effects.

Also, there was a slight difference in demographics between the 005 study and the 006 study. Remember, the 006 study was predominantly African American, and I think relatively young.

CHAIRMAN MASSIE: Okay. Well, let's move on to question 2: In 006 they enrolled patients with severe hypertension, many of whom had signs of ongoing end organ damage, and they received fenoldopam at doses of .01 to .03, at least to start out with, I think it's fair to say.

Did this study identify a minimal effective infusion rate for an antihypertensive response?

DR. LIPICKY: Again, that's not clinically significant. That is an antihypertensive effect.

DR. WEBER: Well, this is, obviously, a somewhat contentious and troublesome spot, because if we take the point of view that the .01 microgram per kilogram dose is in essence a placebo dose and the .03 dose, which really doesn't look very different from it, is the first real dose, I would not regard the .03 dose as really producing an antihypertensive response by any criterion, let alone meaningful response.

So the lowest dose where I would say yes, I'm impressed that this really is having an effect on

blood pressure would be the .01 dose.

DR. LIPICKY: So that means that the dose response in severe hypertension is different from the dose response in the less severe hypertension. Is that your conclusion?

DR. WEBER: That -- Well, yes, that is my conclusion, but the point, of course, was that the less severe hypertensives had a true placebo group, and that placebo group had no effect, and it was truly a zero line. If you could draw a zero line across the data we're looking at here, then everything would look very, very impressive, and this is what you and Bob had wrestled with with the previous submissions of several years ago, that in the absence of a good placebo, it's very, very difficult to know what you're looking at.

DR. LIPICKY: But you do want to draw the conclusion that the dose response in severe hypertension is moved to the right? That's what you said, and I just want to be sure that that's what you mean.

CHAIRMAN MASSIE: Ray, I'll argue the opposite. I think it shifts it to the left, and I don't think I would -- I would not arbitrarily accept .01 as a placebo in the fact that we're seeing

something and makes sense to me that a drug -- and a dose that might not lower blood pressure at all when you start off at 150 might have a more detectable response when you start off at 230.

If you focus on the systolic, I'm also fairly convinced that .03 is a little bit more than .01. So even if .01 is a no-effect thing, that there is something at .03, although the diastolic which I know Mike had opened, doesn't look that way.

I think we have more sensitivity to detect effect on the systolic, since it's so high.

DR. LIPICKY: Well, so there's a slight difference of opinion. You might vote on that.

CHAIRMAN MASSIE: We could vote on that. Anybody else want to address it?

DR. KONSTAM: Yes. I mean, I certainly couldn't say that we have evidence that the pharmacodynamics differ in these two populations. We have no evidence to that effect. We're comparing two different trials and asking what can we get out of those two different trials.

You know, what I hear Dr. Weber saying is that, you know, he can't be convinced from the severe study that the .03 dose works, lowers blood pressure; but part of the problem there is that there's not a

placebo. So that's different from saying that we have evidence that the pharmacodynamics differ in the two populations.

In fact, I would argue, although I can't -- You know, I'm not sure how I can prove it, but my own Gestalt is that they're more similar than different, and I think actually that's what Mike said to the answer to the first question.

CHAIRMAN MASSIE: Anybody else have a feeling whether or not these doses below .1 send a signal of some type?

DR. RODEN: Wasn't there a dropout rate in the people in the more severe study during a run-in phase, number one? Number two, I have a sort of general comment that -- for Ray or for Bob Temple, who is not here, that there was the comment made that you can't use placebos in these kinds of trials. Yet we're making the implicit assumption that .01 is a placebo, and the agency should sort of think about that as a separate discussion.

Number three, in the absence of a placebo, you're -- Ray is going to ask us to vote on a question for which there is no data -- that there are no data. We're perfectly entitled to opinions, but I have no opinion in the absence of data.

DR. LIPICKY: Well, yeah, but I would differ a little bit with what you just said. There is some data. You have a good placebo control dose response curve in one setting.

DR. RODEN: And not in the other.

MR. LIPICKY: Okay, and you have a baseline control dose response curve in another setting, and they look like they're the same to me. So the question sort of comes down to it is a judgment call, and I agree 100 percent there is no data, and the rest of the world doesn't agree, but I think you could do a placebo controlled trial, but nobody else will let you.

So the question is: Do you want to make the judgment that the dose response is the same or not?

CHAIRMAN MASSIE: I really think that it's quite clear to me in systolic blood pressure, you have a 20 millimeter drop from baseline at .03, and whatever we decide about .01, this is different from .01. So I'm not sure I could say that .01 doesn't do anything, but I feel fairly comfortable that .03 does something. Then that's what you want, a visual impression, after all.

DR. WEBER: But the baselines are

different in the two groups.

CHAIRMAN MASSIE: No, but -- I just did -- That's 208. That's 190.

DR. THADANI: Barry, if you look at the baseline pressure in .01 it's higher.

CHAIRMAN MASSIE: No, I understand, but --

DR. THADANI: So if you take that into account, I think there's no difference between .01 and .03, and in that sense of placebo, this could be true effect. If the placebo is a flat line, I think the dose responses in the pharmacodynamic and these are identical in my eyes. I don't think you can say that the responses are different.

DR. WEBER: But, Udho, we already saw that these patients, even before they started the infusions, were drifting down. That doesn't prove that they kept on drifting down, but that is -- I think most of us with experience in dealing with hypertensive emergencies know that, once you put the patient to bed, that the blood pressure starts drifting down.

DR. THADANI: But you could say the same for other hypertensives.

CHAIRMAN MASSIE: I don't want to argue. Will you take this uncertain discussion as an answer

to your question?

DR. THADANI: I think that, to me, they're the same response.

DR. LIPICKY: Yeah, that's fine.

CHAIRMAN MASSIE: Okay, good. The conclusion is that there might be an effect at the low dose, depending on which way you look at it and by whom, because we really don't have anymore data.

So if so, to what populations should this finding be expected to apply? We've sort of gone into that. I think we don't need to do that.

Identify a maximal infusion rate above which the effect was unsafe or intolerable.

DR. WEBER: Well, strictly speaking, it didn't. Again, we believe that there is a dose dependent effect on heart rate, but the reply we got from the look that the folks from Neurex took, there didn't seem to be much of a dose dependent effect on other side effects within the 006 study.

Again, when you look at the efficacy data, there doesn't seem to be a huge increase in efficacy. No, I take that back. There is an improvement in efficacy when you go from .1 to .3. So we really don't know where this might have max'ed out, and I guess the answer is we really don't know where to

stop.

CHAIRMAN MASSIE: Where to stop?

DR. WEBER: Yes. I mean, maybe .6 would be better or potentially it would still be an acceptable dose.

CHAIRMAN MASSIE: I guess the answer, from all the discussion we had earlier, some balance between heart rate and blood pressure lowering that may depend on the individual patient and underlying conditions, their heart rate response, and what blood pressure we're trying to lower from, but it certainly looks to me like the heart rate response gets -- It goes up faster than the blood pressure response goes down lower after you get to that point.

DR. LIPICKY: But the answer to the question is no.

CHAIRMAN MASSIE: Yes.

DR. LIPICKY: And, therefore, to what population does this "no" apply is irrelevant.

CHAIRMAN MASSIE: Going on to 3: Are there data that clarify the relationship, linear or otherwise, between the infusion rate of fenoldopam and its steady state plasma concentration?

DR. WEBER: I think the data that Dr. Taylor showed were actually very tight, and I think

the answer is yes, especially based on the 05 study. I don't know if we need to go further than that. In fact, I thought there was tremendous proportionality between --

CHAIRMAN MASSIE: But 3(b) is in hypertensive crises, but I do remember you saying that the dose -- when you did do those doses, the dose plasma level was about the same in the two groups.

DR. LUTHER: That's correct.

CHAIRMAN MASSIE: So maybe we can move on to 4, much more difficult: Are there data to clarify the relationship, linear or otherwise, between the infusion rate of fenoldopam and its steady state antihypertensive effect?

DR. WEBER: Let's have a look. There is -- Yeah, I think that the data are pretty good, especially if we're talking 4(a), in noncrisis hypertension. If you look at Table 1 of the background book from the FDA --

CHAIRMAN MASSIE: The first book, page 10, right?

DR. WEBER: Yes. Table 1 shows actually very nice relationship between the infusion rates and the antihypertensive effect in the range .04 to .4 at one hour and 24 hours, and muting at 48 hours as the

high doses become a little less effective.

I guess you could say that it's not a tremendously crisp relationship, but certainly at one hour and -- which, I guess, is probably the area of interest, the early part of the study or for the early part of the infusion, there is pretty good proportionality, certainly going from zero up to .4.

CHAIRMAN MASSIE: It sure looks persuasive, though, that something is happening over time, and that both the heart rate effect and the blood pressure effects are going on. It looks like sort of tachyphylaxis, doesn't it?

DR. LIPICKY: But that's not true in the emergent population. Right?

DR. THADANI: Well, the data is only four hours in the emergent population.

CHAIRMAN MASSIE: Going out to 48 hours you lose all that nice response in the emergent population.

DR. WEBER: It's a shorter study, yes, but the answer to 4(b) is pretty much the same as for 4(a), that at least there is relationship between infusion rate and the steady state antihypertensive effect, though I guess you could argue, not quite in steady state during the first four hours.

DR. THADANI: Can you really say that, because the pressure is still decreasing at three and a half hours. So how could you say there's the same relationship?

DR. WEBER: It's sort of between three and a half and four hours, Udho.

DR. THADANI: That's the only time of observation we have. So the peak effect is at four hours. I don't know if you continued eight hours the pressure wouldn't decline further. They're not showing any data.

DR. WEBER: No, but I would be willing to say that at four hours .1 is better than lower doses, and .3 is a little bit better than .1, given all the complexities of that study.

CHAIRMAN MASSIE: It's difficult to read these, even when you design a study that specifically is going to ask these questions, isn't it?

DR. LIPICKY: Because time is limited, you can skip 5.

CHAIRMAN MASSIE: Okay. We're on to 6: Is there data that identified time to pharmacodynamic steady state -- that is, the time to steady state antihypertensive effect for various infusion rates of fenoldopam in first one and then the other group?

DR. WEBER: Well, this was something where I was not thrilled, because -- I guess because the drug worked relatively so quickly, and I would need to be prompted now. Certainly, by one hour we had what seemed to be a steady pharmakinetic state.

I would need to be prompted, though, to see the data that suggests that maybe by 30 minutes, which is the claim of Neurex, that there is some sort of steady state that would allow you to make some sort of decision about altering the dose, but the 05 data suggests, certainly, at one hour we have reached a point at which you could identify steady state antihypertensive effects for different infusion rates.

Now, Ray, when you say is this a meaningful goal, do you mean is this something that's important to know? I think the answer is yes, because if you're the doctor in the emergency room, you need to know how long you should wait before turning up the infusion rate.

CHAIRMAN MASSIE: Okay. Without any further comments -- What about in the hypertensive crisis?

DR. WEBER: Well, I think this is the group in whom this is the most meaningful goal of all, and we only have the 06 study to look at, and of

course, all we see when we look at those data, at least the data we've been playing with so far, is that there is that nice continuing downward trend in blood pressure.

I'm not sure if that's a reflection of the ability of the investigators after the first hour to up-titrate or whether it means that we are observing a continuing downward drift. I really -- We do not have a nice steady state anywhere until we get to about three and a half hours.

So I guess there's going to have to be some empirical decision making by the clinician.

DR. LIPICKY: Yeah, but I guess, if I'm interpreting what you're saying, you're saying the time course should be measured in hours, not minutes.

DR. WEBER: I believe so, yes.

DR. LIPICKY: .5 hours is, you know, in hours, but it's not minutes, even though the half-life is five minutes.

DR. WEBER: That's correct. That is absolutely correct.

CHAIRMAN MASSIE: Although it does look like, if you look at the two higher doses, that if you're going to say that, it's at least a two-compartmental model where there's a rapid decrease in

the first hour, and then a more gradual decline in the subsequent hours, such that you know -- Again, only at the two higher doses, you know a high proportion of the change you can expect at four hours from what happened for the first hour.

I guess that's the way we treat many drugs when we're trying to go between dose and clinical response. If we know that we see most of it -- and the blood pressure is still 185, and you want it down, you would feel comfortable -- I'd feel comfortable going to another dose at that point.

DR. WEBER: Yeah. Nevertheless, if you look at the 0.1 dose, which is the dose that Neurex has suggested would be a starting point, at 15 minutes something has happened, at 30 minutes a little more, at 45, and on to an hour, it does seem to be drifting on downwards, though I guess you could argue that most of what happens, as Barry just pointed out, did take place in the first 15 to 30 minutes.

CHAIRMAN MASSIE: Oh, I was actually arguing first hour. I was looking at the systolic again, but it's some time faster than several hours.

DR. LIPICKY: Time constants in the order is measured in hours.

DR. WEBER: Yes.

DR. LIPICKY: Not minutes.

DR. WEBER: Not minutes. Right.

CHAIRMAN MASSIE: Okay. I guess we should go on. Are there data to characterize the time course of decline in antihypertensive effective of fenoldopam after discontinuation of the drug?

DR. LIPICKY: And since time is limited, you can skip that also, if you would accept the fact that it could be characterized in minutes.

DR. WEBER: Yes, very, very few minutes, in fact.

DR. LIPICKY: Fast, yes.

CHAIRMAN MASSIE: Good. Then the next question has to do with metabolism. Do you want us to touch on that?

DR. LIPICKY: Yes.

CHAIRMAN MASSIE: Okay. It can be metabolized by any of several hepatic pathways and plasma clearances not materially affected by cirrhosis or renal disease. These facts reduce the likelihood of drug/drug interactions, but are there data to describe or rule out organ dysfunction induced alterations in fenoldopam's antihypertensive effect?

DR. WEBER: Well, I guess the answer to that has to be, no, we don't have as much data as we

would like to look at every possible organ. I thought the data from the renal study at least showed that, functionally, during the periods of infusion there were no adverse organ effects.

I don't recall seeing anything in the database or with any of the side effects that would make me believe that there's a metabolic issue here.

DR. LIPICKY: So, I mean, that question was really meant to elicit whether, in the presence of renal disease or hepatic disease, there had to be an alteration of the dosage recommendations.

DR. WEBER: I would say, as far as I can see, no.

CHAIRMAN MASSIE: Okay. QT, question 10: In one study, B-74, the fenoldopam seemed to prolong the QT interval more than sodium nitroprusside control. Perhaps relatedly, one patient with congestive heart failure in an early fenoldopam study developed ventricular fibrillation and died. Is fenoldopam's putative effect upon the QTc interval of substantial concern?

DR. WEBER: John promised he would help me with that.

DR. DiMARCO: I think the data really don't allow us to definitively answer that. There is

some prolongation of the QT interval. It's pretty minimal. It doesn't -- It wouldn't be surprising, but to comment ont he safety in this database, when you only have one event and in the 06 study you really only have 100 patients, it's really hard. It's probably not very frequent, but I don't think you could rule out any significance of it.

CHAIRMAN MASSIE: Anybody else concerned about the QT effect, more so than the cautionary statement that we can't rule it out?

DR. LIPICKY: Maybe I should ask just a little bit of clarification. Does that mean that this is a worry and that people should worry about it and incorporate it into their thinking process and/or put limits on the QT at baseline before giving the drug, and watch it and monitor it?

DR. DiMARCO: Well, in fact, in the study, if you look at the baseline QT intervals, they're pretty long in this group, to start with. So if anything, I'd be a little reassured. So I'm saying I'm not concerned, but I don't think we have enough information to rule out some low frequency event, but I would not -- I don't think this would be a major concern at this point in time.

DR. THADANI: Does that mean you want to

repeat a ECG before every dose titration?

DR. DiMARCO: Well, I think that the indication -- This is going to be used mostly in a monitored setting, and so I think that you would monitor that. I'm actually not that particularly worried that you would have --

DR. LIPICKY: You can't measure a QT interval on the monitor.

CHAIRMAN MASSIE: You can detect arrhythmias.

DR. LIPICKY: Well, you left me just a little bit unsettled. I'm sorry to keep barging in, but you sort of said I don't know. So then you got to write a label, and the question is do you think "I don't know" means it's a problem and people should worry about it, or "I don't know" but it doesn't look very real, so maybe mention it somewhere?

DR. DiMARCO: If I were going to pick the two, I'd pick the latter.

DR. LIPICKY: Okay.

CHAIRMAN MASSIE: It didn't look like much of a signal at all there, and I don't know if you can relate a sudden death from someplace else, some other time, in a population where they're lucky if they only had one v. defib patient. That would be my thought.

Are there any other adverse effects of concern when fenoldopam is administered intravenously to patients with hypertension? I guess we've heard concern on heart rate.

DR. LIPICKY: And ischemia.

CHAIRMAN MASSIE: Well, but implicitly, I guess, is the issues, if you raise heart rate.

DR. LIPICKY: I think you have really pretty well discussed that already, unless you want to add some other items to the list.

DR. KARKOWSKY: There have been a couple -- This is Dr. Karkowsky from the FDA. There were some episodes of increase in creatinine that were more than trivial that occurred on or after fenoldopam infusion. That's number one.

The other one is there's a substantial drop in potassium, at least during the first six hours of infusion, and to some extent that might explain some of the changes in EKGs, but it seems to be independent -- it seems to be something that is probably worthy of putting in the labeling, from my vantage point.

DR. CALIFF: Can you clarify what you mean by substantial?

DR. KARKOWSKY: .4 or equivalence per

deciliter within the first six hours, a substantial number of people with potassiums below 3.

DR. CALIFF: So it's an average of .4, a medium?

DR. KARKOWSKY: -- drop for group, yes.

DR. CALIFF: So there were some that were much greater than that.

DR. DiMARCO: Yes. Some of the people who had the longest QT interval had drops of almost a milliequivalent.

CHAIRMAN MASSIE: Was that different when you analyzed it from the nitroprusside comparators, because it looked like they had a substantial drop in potassium in some cases, too.

DR. KARKOWSKY: The sponsor would have the data for the nitroprusside more on the tip of their tongue than I would. There was some, I think, that was greater in the fenoldopam, but I can look up what I've got in my reviews.

CHAIRMAN MASSIE: Actually, I don't think it makes any difference for labeling, because if it happens, it happens, and people ought to be warned about it even if it's not different from another drug.

DR. WEBER: Right.

DR. KONSTAM: Can I just ask Ray, what

wording, if any, would you consider regarding the concomitant use of beta blockers?

DR. LIPICKY: Well, I would argue that the use of beta blockers should not occur, period, in association with fenoldopam until there is some data that would say that it doesn't really alter the dose response relationship very much, considering -- once you start writing instructions for use, because it really would bother me if there were beta blockers on board or added.

CHAIRMAN MASSIE: Well, is the question dose response or safety?

DR. LIPICKY: Well, I don't know what the safety implication is. It would seem to me to be dose response. That is, if it is more antihypertensive in the presence of beta blocker because you do not have the reflex tachycardia, that would raise the safety issues; and then, in fact, the instructions for use that would be written from the data that are available would be not applicable.

CHAIRMAN MASSIE: Can I ask you whether we have dose response data in this type of setting with any drug on top of any background therapy?

DR. LIPICKY: For intravenous therapy, you mean?

CHAIRMAN MASSIE: Yes. In other words, do we really have that for nitroprusside?

DR. LIPICKY: No.

CHAIRMAN MASSIE: Do we have it for IV Nicardipine?

DR. LIPICKY: No, but you guys have worried the bejesus out of me about this.

DR. KONSTAM: You know, Ray, you know, I can't disagree with what you're saying, based on the fact that there are no data. I just want to comment that, you know, I think that this poses a remarkable quandary, you know, to the clinician who will be extremely tempted to use it in conjunction with beta blockers and, conversely, if the clinician were to take that warning seriously, I think he or she would have serious reservation about using the drug.

DR. LIPICKY: I understand, but if a physician wanted to use a beta blocker in association with fenoldopam, they ought to apply for an IND.

DR. KONSTAM: May we advise the sponsor to consider doing a study with concomitant use of beta blockade?

DR. LIPICKY: In malignant hypertension?

DR. KONSTAM: Well, I guess that's a separate question.

CHAIRMAN MASSIE: Well, it wouldn't hurt to start with somebody, malignant or not.

DR. WEBER: Yeah, I don't think you would need to do it in malignant hypertension. I think you could do a relatively small number of patients in whom you can induce tachycardia and see if, by giving a beta blocker, you exaggerate the blood pressure effect. That shouldn't be difficult to do.

DR. LIPICKY: Well, it's not an unreasonable suggestion. It might be useful to show the strength of the committee's will there by voting yes or no, they should be asked to do that or not?

DR. WEBER: One of the problems, Ray, is that, of all the drugs that these patients were transitioned to in the oral phase -- they had plenty of experience with calcium blockers and others -- somehow beta --

DR. LIPICKY: Well, I hear you. Just take a vote on that, yes or no, so we know whether that's one guy or everybody.

CHAIRMAN MASSIE: Okay. I think we've -- People have raised this concern. So I guess the question is some data, maybe short of a formal dose response curve in malignant hypertension, but an experience to show whether it's as safe and not

markedly different, I guess, to treat hypertension with this agent with beta blockers around. Is that -- Okay. We should have a vote.

I'll start down at the left here.

DR. THADANI: I think we need more data. In that sense of data, I can't say anything.

CHAIRMAN MASSIE: No, we're asking whether we think that there should be more data. Yes or no?

DR. THADANI: I think a study is required, yes.

DR. DiMARCO: Yes, I think we need more data as well.

DR. GRINES: I think it would be nice to have this kind of data with all antihypertensive drugs, but I'm not sure that we've required other formulations to do a study specifically with beta blockers or ACE inhibitors or calcium blockers or anything. So I think this is a rather new recommendation.

DR. KONSTAM: Can I clarify what we're voting on?

DR. LIPICKY: Is that a no?

DR. GRINES; That's a no.

CHAIRMAN MASSIE: The question is: Do we feel that we need data on the interaction between this

drug and the beta blocker before we're going to approve it?

DR. KONSTAM: Oh, well, no, no. That's not the question.

DR. LIPICKY: Well, that's another question which would come after your yes or no.

CHAIRMAN MASSIE: Okay, what is the question? Do we just want more data?

DR. LIPICKY: Do you want them to do a trial? That's the question.

CHAIRMAN MASSIE: Okay. Do we want them to do a trial which gives us some information about the combination of fenoldopam and beta blockade?

DR. GRINES: Prior to approval?

DR. LIPICKY: No, no, no. That's another question.

CHAIRMAN MASSIE: So this is --

DR. WEBER: Can we vote on both at the same time, say yes, I'd like more information, but no, I don't need it --

CHAIRMAN MASSIE: No, let's do it Ray's way. Ray likes process.

DR. GRINES: Okay. Well, then I'll change my answer to, yes, I would like to see a trial.

DR. WEBER: Oh, sure, I'd like to see

data, too.

CHAIRMAN MASSIE: I would as well.

DR. KONSTAM: Yes.

DR. CALIFF: It's hard to imagine what clinician would use the drug without having a little bit more information than this.

DR. LINDENFELD: Yes.

DR. RODEN: It's impossible to vote against Mom and apple pie.

DR. MOYE: I agree. More data is needed.

DR. LIPICKY: So then you have to say before approval or after approval, and that's a simple answer, too. All you have to say is before or after.

DR. GRINES: Can I ask a question, though, Ray, because it's always confusing to me to talk about thrombolytic trials which have tens of thousands of patients, then shift gears and go to these antihypertensives; because it seems that many of them have been approved with very small numbers of patients studied.

Is this number of patients out of line with other antihypertensive drugs?

DR. LIPICKY: Well, no. This is digression from the question you're supposed to answer, but I will answer it.

The antihypertensive drug approval is based on a surrogate of blood pressure. Now it's possible to make that change -- okay? -- and that's been a long discussion, and perhaps it ought to be a longer discussion, but it's based on pharmacological effect.

That comes from the fact that a number of different classes of agents that share hypertension -- antihypertensive effects have been shown to have clinically meaningful effects in placebo controlled trial, and that it seems impossible to get another placebo controlled trial in that setting, and that the setting that one could do a positive control trial in is not present.

That is, there is no single agent nor even combination of agents that you could have -- that there are enough trials for to be able to do a placebo controlled trial -- I'm sorry, a positive controlled trial like thrombolytics do, because there's a placebo controlled background for that.

So it is just on the basis of blood pressure effects alone. We are very concerned, since that's true, that risks be not potentially present, because the incidence of good things is something like a few per thousand patient years. Okay? Those are

the good things.

So it wouldn't take a very large bad effect to have really very bad -- There would be no net change. So we're very concerned about that. In emergency hypertension and the malignant hypertension setting, my bias is nobody knows what they're doing, but nobody would allow blood pressure to stay at 140 with new flame hemorrhages for a very long period of time.

It is true that one knows in that setting other drugs do change clinically significant effects, if the blood pressure is lowered. So we're willing to accept that there, too, but we don't have any event driven knowledge.

CHAIRMAN MASSIE: I think what -- Let me just express the concern that I sense and I share, which is that there is no such data for other drugs, and there is a sense of fairness here, I guess, although amongst people here wondering what we're requiring, which hasn't been required before, intellectually that may not support anything.

I do feel the field has shifted. They approve drugs that I consider dangerous in certain patients for this very indication, and then there are unapproved drugs that I consider dangerous for this

indication, and the danger is ischemic events, and the marker of it is tachycardia.

So although I guess we don't have this data anywhere, the total absence of any knowledge of what happens to the drug that I would use in the presence of a tachycardia if I wanted to use this drug is of great concern to me.

I guess my second question -- and this is to Ray -- is: How hard is it going to be? That's why I say a dose response curve in malignant hypertension is basically starting the program over again and probably, I think, unnecessary; but what about getting experience with the combined use of the drug so --

DR. LIPICKY: Well, that would have to be an event driven trial.

CHAIRMAN MASSIE: No, no, no, no.

DR. LIPICKY: Okay. If that's --

CHAIRMAN MASSIE: I'm talking about --

DR. LIPICKY: -- experiential data giving an answer to a safety question. If you have a real safety concern, that has to be a controlled trial that's event driven. Otherwise, I'll continue to deal with the phenomenological level.

CHAIRMAN MASSIE: Okay.

DR. LIPICKY: So it's a matter of what is

the level of concern, because I can't make a decision about whether or not T-waves going up or down is important unless I count MIs and/or death.

CHAIRMAN MASSIE: I think maybe we're talking about something different. We're talking about the fact that many clinicians will use this combination.

DR. LIPICKY: Well, I understand.

CHAIRMAN MASSIE: Not illogically.

DR. LIPICKY: So what is it you want to know?

CHAIRMAN MASSIE: We want to know what happens when you use this combination.

DR. LIPICKY: What do you mean, what happens? Does the dose change?

CHAIRMAN MASSIE: Heart rate, blood pressure.

DR. LIPICKY: Does the dose change? Is that the question or you don't care about that?

CHAIRMAN MASSIE: Actually, I'd just like to know what happens to the heart rate.

DR. LIPICKY: In the presence of a beta blocker?

CHAIRMAN MASSIE: Yes. I'd like to know whether it blocks the tachycardia --

DR. LIPICKY: So you would study a single dose in the presence and absence of a beta blocker and stop there?

CHAIRMAN MASSIE: That's what I was thinking of, yes.

DR. KONSTAM: Well, Ray, you said earlier that you would put in wording that warned against the concomitant use of this agent and a beta blocker. Why did you say that, and what --

DR. LIPICKY: Because I'm not sure that the instructions for use that will be able to be written will be the same in the presence of a beta blocker, because the tachycardia must do something with respect to the --

DR. KONSTAM: Right, but in terms of dose response, for example.

DR. LIPICKY: Right.

DR. KONSTAM: So I guess that would be my answer to you, is: That type of information would need to come. That is, for example, what would be the impact of concomitant beta blockade on the dose response and the pharmacodynamics of the drug?

DR. LIPICKY: I'd be comfortable with that, but that's not an event driven trial. It presumes that, if the dose response stays the same,

whatever is satisfying safety-wise now would be equally satisfying or, if the dose response changes and the instructions for use are modified, that then that would be also equally satisfying; but it would not be able to tell whether T-waves going up or down meant anything at all.

DR. CALIFF: I'm not satisfied with that, but you know, this issue of fairness and where our responsibility lies, I think, is a key focus of the discussion. Seems to me that we're lowering the blood pressure to prevent stroke and myocardial ischemic events and renal failure, and that we could easily lower the blood pressure in a variety of different ways and have very different effects on those things that we're really trying to prevent.

So doing these little tiny studies with these little tiny endpoints doesn't really seem to give us the answers that we need to know what to do to protect the interest of the public.

DR. LIPICKY: Well, what would you be comfortable with?

DR. CALIFF: Well, an ideal study might -- Since this seems to be a surrogate for nitroprusside in many ways -- would be a fairly large study comparing it with nitroprusside. I'm not very worried

about dose response, because the way this is going to be used is like nitroprusside.

You start at a dose, and you dial it up and look at the heart rate and blood pressure, and change your dose based on what you see.

DR. LIPICKY: But this is -- Now this is the beta blocker issue. So it would be nitroprusside with and without beta blockers, fenoldopam with and without beta blockers?

DR. CALIFF: Well, with enough patients you would have some who would get beta blockers. You could do that in a factorial design to give you that answer.

DR. LIPICKY: But it would be the equivalent of at least a four-arm trial.

CHAIRMAN MASSIE: Rob, you're an expert on this. Give us a sample size calculation here.

DR. CALIFF: Well, I think Ray's most important statement was that nobody knows what they're doing in this disease, because we don't know what the event rates are with any of the treatments. You would have to start out with a guess on the sample size, which would be driven by some estimate from some study that I haven't seen yet of what the event rates are.

CHAIRMAN MASSIE: Probably a few thousand.

DR. CALIFF: Maybe a couple of thousand would do.

DR. KONSTAM: I'm very sympathetic of Rob's perspective, but I think that I, for one, clearly would not want to ask this sponsor, you know, to do this. I think that I would be comfortable for the moment, in terms of acute hypertensive therapy, looking at the blood pressure as a surrogate for -- or a control of blood pressure as a surrogate for the benefit, and conversely, the tachycardiac response as a surrogate for bad things happening.

In that context, I think -- You know, when I raised the concern, I was raising, you know, concern with a practical eye, which is that people will want to use beta blockers together with this, and we don't know how to use beta blockers together with this drug, and we need some pharmacodynamic information.

DR. LIPICKY: Well, this could be a very long discussion. I think all of the stuff has been laid out. All I'd like to get now is before or after, from every mouth.

CHAIRMAN MASSIE: Okay.

DR. THADANI: I think we should get experience after, because if you apply this applicable to everything you do in life, and the data --

CHAIRMAN MASSIE: Before or after?

DR. THADANI: After.

CHAIRMAN MASSIE: Before or after?

DR. DiMARCO: I am concerned about the fairness issue, but I'd like to get more data before.

DR. GRINES: I guess it depends on whether we're talking about a mega-trial, which I think is going to be particularly difficult to recruit into. I think that many of these patients with hypertensive emergencies have heart failure, and it's going to be hard to give them a beta blocker, and it's going to be hard to consent those patients.

So I don't have a problem with getting pharmacodynamic information, but not in this particular patient population, necessarily.

DR. LIPICKY: Before or after?

DR. GRINES: Before.

DR. WEBER: After. I would like to know a little more about this, and I don't need to do any fancy studies. I think, if I knew what would happen to someone who is on fenoldopam and they were then given a beta blocker on top of it, and was there a precipitous change in blood pressure or was there, in fact, on heart rate, those would be interesting things to know.

I wouldn't need to do complicated studies at all, just to ask that very question the simplest possible way, but after is my response.

DR. LIPICKY: Did you say after?

CHAIRMAN MASSIE: He said after. I mean, that's why we can't distinguish the nature of the study from the answer, but I don't want to see this drug without any knowledge at all. So I'm going to say after. I'm sorry. You can see how conflicted I am on this. Can't even say the right answer. I mean before, yes.

DR. KONSTAM: Yes, I raised this question, and now I'm feeling a little guilty about it, because I think that this is an approvable drug. I think it does what it is that we want it to do, and it's going to wind up being severely handcuffed by the warning about beta blocker therapy.

So I want the data, but I think it's an approval drug, and I would say after.

DR. CALIFF: I guess under the current set of rules, I think it would be really good to see a small study before, not necessarily in severe hypertension, just for some reassurance. That would be an easy thing to do, but I hope the rules will change prospectively soon.

DR. LINDENFELD: I think, after.

DR. RODEN: After.

DR. MOYE: Before.

DR. LIPICKY: Okay. Thank you, that's fine.

CHAIRMAN MASSIE: Okay. You don't even want to know the numbers?

DR. LIPICKY: Well, Joan has them written down.

CHAIRMAN MASSIE: We've got a mixed sentiment here, which tosses it back into your ballpark.

DR. LIPICKY: No, that's fine.

MS. STANDAERT: There are ten of you. It's five/five.

CHAIRMAN MASSIE: Five/five. Ray, you get to decide.

DR. LIPICKY: So you have some more questions.

CHAIRMAN MASSIE: Okay, 12: Should fenoldopam be approved for the treatment of hypertension when oral therapy is not practical? If so, how should the indicated population be identified in labeling, and what should the labeling say about the transition from fenoldopam to oral medication?

DR. WEBER: Well, the answer to the first part is yes, it should be approved for the treatment of hypertension when oral therapy is not practical.

How should the indicated population be identified? I don't think that it should be identified. I don't know if any of the other drugs that are used in this way identify a population, because clearly, different physicians in different settings have different criteria for wanting to use an antihypertensive drug parenterally.

The only way I could see this being important is if there were a subgroup of people that we would wish to exclude from this form of treatment, and right now I can't think of any particular group. So I would just keep it as very simple labeling, the way it says in the first phrase.

As far as the transition from fenoldopam to oral medication, right now I would basically recommend that, once the blood pressure was stable, that oral therapy should be started cautiously; and again I would follow labeling that I assume we've already gone through for the other drugs of this type.

I guess, if we approve it and we don't have the beta blocker data, it might be important to caution that, when beta blockers are used as the first

treatment for the hypertension, in making this transition they should be used with caution, at least initially.

CHAIRMAN MASSIE: Any other discussion on this point?

DR. RODEN: If we -- I mean, Ray drew the distinction between antihypertensive therapy for the surrogate endpoints of stroke and myocardial infarction, renal failure and antihypertensive therapy for accelerated hypertension or malignant hypertension. Those are two sort of separate issues.

So are we voting --

CHAIRMAN MASSIE: We're voting simply on the first of the potential indications, which is just for people who can't take oral medication, should this be approved as a substitute, not the malignant, accelerated, urgent, because there were two indications proposed, and this is that one, presumably somebody going to surgery or somebody who has intestinal obstruction, is NPO or whatever.

Okay? We get the picture? Lem.

DR. MOYE: I would vote for no approval, and I would vote for no approval, because, number one, I'd like information on the use of this medication with concomitant agents.

Secondly, I'm uncomfortable with the analysis that's been carried out for the dose response relationship. It isn't clear to me how we could have a study designed to look at dose response that doesn't give us a maximal dose.

Thirdly, I continue to be uncomfortable with the size of the database we're using here to base a conclusion on. Unfortunately, there were no standard errors or standard deviations provided for the effect sizes. So it's very difficult to judge the relative efficacy one dose of another.

I put that all together. For me, that comes down to no approval.

CHAIRMAN MASSIE: Dan?

DR. RODEN: I'm uncertain about this indication, and I guess I would vote yes for this indication, assuming that there was something in the labeling that outlined the clinical circumstances under which one would use it, as opposed to just say that this is indicated for intravenous therapy of hypertension, without some description of those kinds of clinical situations.

So I don't know whether I voted yes or no, but Ray is nodding. So I guess I'm voting yes.

DR. LINDENFELD: I would vote yes. I

would like to see something in the precautions noting the reflex tachycardia. I find it hard to imagine very many circumstances when this would be indicated, but it does seem to lower blood pressure in this population.

DR. CALIFF: I say yes, too, mostly just out of tradition that this is -- that the stuff lowers blood pressure, and that seems to have been the standard, which doesn't seem to me like a very good standard, but that's what we have.

DR. KONSTAM: Yes.

DR. WEBER: Yes.

CHAIRMAN MASSIE: Although the population thing is, I would say, in patients in whom reflex tachycardia or tachycardia was not contraindicated. Mike?

DR. WEBER: You already have my yes vote.

DR. GRINES: Yes, and I agree with Barry's recommendation on labeling.

DR. DiMARCO: I'll come down on yes, I guess, if the only criteria, does it lower blood pressure, I think it lowers blood pressure, and you could safely do that, at least in terms of just lowering blood pressure. I still have some questions about the size of the dataset, though.

DR. THADANI: My answer is yes, and obviously, it will depend on the physician, if he wants to lower the pressure. It has to be up to him.

CHAIRMAN MASSIE: Okay. We're down to the last question. Should fenoldopam be approved for treatment of severe hypertension, malignant hypertension or hypertensive crises?

Do you want us to pick which one of those or you can do that?

DR. LIPICKY: No. We'll do that. It's those kinds of things. It differentiates it from if people can't take it orally. It makes an indication, a real indication.

CHAIRMAN MASSIE: Maybe we'll save who the population should be until after we vote yes or no on this question?

DR. LIPICKY: Sure.

CHAIRMAN MASSIE: Mike, do you want to give the first vote?

DR. WEBER: Yeah. I must say, without getting into the semantics of severe versus malignant or crisis, the fact is I would say that throughout the experience with this drug they have given it to people with very high blood pressure, and they've given it to people who had some kind of a symptom or a finding

that went along with a high blood pressure and would, by different ways of defining these things, be called malignant hypertension or a hypertensive crisis, and the drug seemed to work very well in most of these patients, not all of them, but it worked very effectively overall and safely.

So I would support approving this. I think, Ray, there is a difference between severe hypertension, which is a pure blood pressure problem, and the more complex patients who were studied in the 06 trial. So I think it would be possible to label it for more than just high blood pressure.

CHAIRMAN MASSIE: Okay. Udho?

DR. THADANI: Yes, with the reservation that I'm not sure how often to increase the dose. My bias is the later, the better, and also reservation of background beta blockers.

So the answer is yes, with something in the labeling. We still don't know how to increase the dose. I'm uncomfortable with every half an hour increase, because of tachycardia at the higher doses.

DR. DiMARCO: I'll vote yes.

DR. GRINES: I'll vote yes, but this is an area where I'm more concerned about the reflex tachycardia, because it requires higher doses of

drugs, and perhaps there should be a warning for this indication.

CHAIRMAN MASSIE: I'll vote yes, too, and I'm assuming that something after today's discussion comes in about the tachycardia will get into the labeling.

I would just say one other thing, because usually -- We haven't really gotten the dose. We've had a lot of discussion. I don't believe the starting dose should be .1 in most patients, but I think you'll be able to figure out how to label that.

So with that proviso, yes.

DR. KONSTAM: Yes, I'll vote yes.

DR. CALIFF: Yes, with the tachycardia concern and the beta blocker concern.

DR. LINDENFELD: No. I just don't think there's enough data in this subset, and I think with the reflex tachycardia there's some in whom it may be contraindicated.

DR. RODEN: My vote will be with everyone else or the majority. So it will be yes, but.

DR. MOYE: My vote is no with the same concerns I had before. We just don't know enough about dose response here.

CHAIRMAN MASSIE: Okay. Are there any

other questions that you want us to address?

Okay, we will try to get together -- how about 1:30? We have a long afternoon, I think.

(Whereupon, the foregoing matter went off the record at 12:58 p.m.)

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A F T E R N O O N S E S S I O N

Time: 1:45 p.m.

CHAIRMAN MASSIE: Could the members of the Committee please come up here, who aren't here yet?

Okay, I think we'll get started again, if everybody could take a seat and stop the conversations, committee and otherwise.

Our second order of business today is to review the NDA for Lovenox, enoxaparin, in unstable angina and non-Q-wave MI. We'll try to follow the same format of letting the sponsor go through their presentation until completion, and then answer questions led by Dr. Konstam, who is our reviewer for this drug, and other members of the committee.

So why don't we get started.

DR. TALBOTT: Dr. Talarico, Mr. Chairman, ladies and gentlemen of the Committee, and FDA staff, good afternoon. I'm Max Talbott, Vice President for Worldwide Regulatory Affairs, Rhone Poulenc-Rorer.

We are appearing before you today in support of our supplemental new drug application for Lovenox, enoxaparin sodium, in the treatment of unstable angina and non-Q-wave myocardial infarction. The focus for our application was the ESSENCE trial, and I will now introduce our presentation.

I will list my colleagues who will be reviewing Lovenox and the ESSENCE study today. Following my brief introduction, Dr. Janet Rush, Rhone-Poulenc Rorer Group Director for Cardiology, will provide an overview of Lovenox. Following Janet, Dr. Marc Cohen of Allegheny University, Hahnemann, will review the efficacy of the ESSENCE trial. Dr. Cohen is also Chairperson of the ESSENCE Steering Committee.

Following Dr. Cohen's presentation, Dr. Gregg Fromell, Rhone-Poulenc Rorer, will review the safety of Lovenox and ESSENCE. Dr. Eugene Braunwald, Hersey Professor of Medicine, Harvard Medical School, will then discuss the clinical impact of ESSENCE. To conclude our discussion, Dr. Rush will then provide a summarizing statement describing the consistency of ESSENCE trial elements with the criteria of the FDA's guidance for the acceptance of a single pivotal trial.

The guidance document is a recent FDA initiative which will figure prominently in our discussion today.

Prior to the remainder of the presentations, I want to briefly trace the development of the Lovenox ESSENCE project.

In August of 1994, we first met with FDA

to design the plans for the Phase III evaluation of the use of Lovenox with aspirin in the treatment of unstable angina and non-Q-wave MI. Based on this meeting and a series of interactions with the FDA over the next 20 months, culminating in a May 9, 1996 meeting with the agency, a development plan was agreed to with FDA.

The agency's medical reviewer, Dr. Sizer, characterizes these interactions in the documents that have already been provided to the Advisory Committee. One result of the May 9, meeting, though, was an agreement that one study would be considered adequate, if an effect were seen in reduction of the double endpoint of death and myocardial infarction.

Results of one additional interaction with the FDA has not been described in your materials. On October 29, 1996, a teleconference was held between RPR and FDA to discuss the results of the ESSENCE trial, which were soon to be presented at the American Heart Association meeting.

Based on Lovenox demonstrated superiority over heparin with triple endpoint and a strong trend with a double endpoint, FDA agreed that the filing of our application with a single pivotal trial was appropriate. The agency stated that, because of the

importance of the results, they would review the application quickly.

This application was filed on March 18 of this year. As you can see from our being here today, the agency has moved quickly on the review of our submission, and we certainly appreciate FDA's timely action on this matter.

We believe that the importance of the results of the ESSENCE trial and a recent agency initiative will lead you toward recommending approval of this application today.

The recent agency initiative to which I refer is the March 13, 1997, proposed guidance document from FDA that, among other things, lists the criteria by which a single, large, multi-center trial such as ESSENCE could demonstrate the requisite safety and efficacy for approval.

This approval can apply to a new chemical entity or, as in the case with Lovenox, to a new indication for a drug that has already been available for a number of years. The elements described in this guidance have already been applied by FDA to a number of approvals prior to the publication of the proposed guidance, and even though the guidance document is itself labeled "Draft," we have been informed by FDA

that the elements of this guidance can also be applied to the evaluation of our application for Lovenox.

As indicated, the proposal by the agency describes the circumstances under which FDA may grant approval on the basis of a single pivotal trial, and in describing the rationale for this single trial, proof efficacy initiative, FDA made the following comment:

"Thirty-five years ago, when the effectiveness requirement was originally implemented, the prevailing study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures and little attention to perspective identification of outcomes and analyses. At present, major clinical efficacy studies are typically multi-centered, with clear perspectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve extreme statistical results, and could often be evaluated for consistency across subgroups, centers, and multiple endpoints."

Continuing, FDA said: "The added rigor, power and scope of contemporary clinical trials have made it possible to rely in certain circumstances on

a single adequate and well controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval."

I will now briefly touch upon the pertinent elements from the guidance document. Then my other colleagues will elaborate on these points during their presentations on Lovenox, the ESSENCE study.

By way of introduction, the FDA guidance criteria for the acceptance of a single study have four primary considerations that touch upon the size and design of the study, potential internal confirmation within the study, verification of the study by multiple endpoints, and powerfully significant findings.

FDA notes that the criteria are themselves not a complete listing, but rather "provide examples of the reasoning that may be employed" in evaluating whether a single study provides adequate proof of effectiveness. The remainder of my introduction will briefly comment on these single study effectiveness criteria in preparation for their more detailed discussion by today's other speakers.

During this presentation we will

demonstrate that the ESSENCE trial was a large, randomized, blinded, multi-center study that is not impacted by the particular results of a single site or country in regard to observed effects.

We believe that the care in the design and conduct of ESSENCE comply with the FDA's guidance regarding the necessary steps to minimize bias in the trial. These steps include the traditional processes noted in this slide, as well as additional steps such as a Clinical Events Committee and ongoing quality assurance monitoring.

The FDA guidance also relies in part on internal correlations that can occur within a single, large, multi-site trial. These comparisons may involve various stratifications or multiple endpoints associated with various outcomes.

Not surprisingly, the FDA guidance document demands a very powerful statistical result on objective endpoints. We believe that our demonstrated superiority over heparin meets the standard for a significant and clinically meaningful effect.

Other elements for reliance on the findings of a single multi-center study are contained in the FDA's guidance document. These are listed in the above slide and will be discussed by today's

speakers in regard to Lovenox and the results from the ESSENCE study.

Perhaps the best way to introduce our discussion then would be to recite from FDA's statement about the guidance document's own discussion of its own proposed criteria, and I quote: "What follows identifies the characteristics of a single, adequate, and well controlled study that could make the study adequate support for an effectiveness claim. While no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an efficacy claim."

I think this clearly summarizes the issue before us today.

We intend to demonstrate why we believe that our supplemental new drug application, and most specifically the results from the ESSENCE trial, meet the FDA guidance criteria for the approval of an application on the basis of a single pivotal trial in support of an efficacy claim.

My colleagues will describe what we believe to be compelling evidence for the approval of Lovenox, enoxaparin sodium, in the treatment of unstable angina and non-Q-wave MI. The first speaker

today is RPR's Dr. Janet Rush, Group Director for Cardiology, who will present an overview of Lovenox. Janet.

DR. RUSH: Good afternoon. Enoxaparin was first approved for the prophylaxis of venous thrombosis in France in October 1987 and approved in the U.S. in March 1993. It's estimated that approximately 34 million patients have received enoxaparin in the 56 countries in which it's currently approved. This includes an estimated 500,000 patients who have been treated for deep vein thrombosis at a dose of 1 mg/kg subcutaneously twice daily, which is the dose being proposed in the current application for unstable angina.

Dossiers for the use of enoxaparin in unstable angina were filed in March 1997, and are currently pending in 19 countries.

Standard, unfractionated heparin is a heterogeneous mixture of heparin chains with molecular weights ranging from five to 30,000 Daltons. Low molecular weight heparins are a class of compounds obtained by fractionating or depolymerizing this mixture into chains which have average molecular weights below 8,000 Daltons.

Enoxaparin has a mean molecular weight of

4500 Daltons. The low molecular weight fraction of heparin has very different pharmacologic characteristics in comparison to the parent compound. Well documented studies over the past ten years have demonstrated that 18 saccharides is the critical chain length which differentiates the low molecular weight chains.

The higher molecular weight chains -- that is, those longer than 18 saccharides or over 5400 Daltons -- demonstrate the characteristics listed on the righthand portion of the slide. Chains longer than 18 saccharides exhibit both anti-IIa and anti-Xa activity. They are sensitive to inactivation by platelet factor IV, bind nonspecifically to plasma proteins and endothelial cells, and are less efficient at inhibiting the generation of thrombin.

The lower molecular weight chains, primarily inhibit factor Xa, are resistant to inactivation by PF-4, are less bound to plasma proteins, and are efficient inhibitors of thrombin generation.

Let's examine some data which address these points further. Probably the most important advantage of low molecular weight heparins is their predictable anticoagulant response. The large

patient-to-patient variability in the dose of standard intravenous heparin required for a therapeutic effect is largely the result of nonspecific binding to plasma proteins, including the acute phase reactants present in patients with acute coronary syndromes.

In contrast, a weight adjusted dose of subcutaneous enoxaparin results in predictable anti-Xa levels. This slide shows the measured anti-Xa levels at peak and trough for 164 patients with unstable angina. At steady state, anti-Xa levels of one anti-Xa unit per milliliter at peak, and .5 at trough, are attained.

By contrast, a continuous infusion of intravenous, unfractionated heparin adjusted to an activated PTT of 1.5 to 2.5 times control generally results in anti-Xa inhibition of between .3 and .6 anti-Xa units per milliliter.

As arterial thrombi are platelet rich, resistance to degradation by platelet Factor IX is probably also an important advantage of low molecular weight heparins over standard heparin in arterial thromboses.

In this in vitro study of the ability of platelet Factor IV to neutralize anti-Xa, anti-IIa, and inhibition of thrombin generation, the anti-Xa

activity of unfractionated heparin, shown on the left of the slide with the yellow bar, was 94 percent neutralized by platelet Factor IV; whereas, anti-Xa activity in the presence of enoxaparin on the right was only 18 percent neutralized.

Similarly, the ability to inhibit thrombin generation, shown by the red bars, was almost completely neutralized in the case of heparin, but only 40 percent neutralized with enoxaparin. As predicted, anti-IIa activity, shown by the orange bars, was neutralized by PF-4 for both heparin and enoxaparin.

The selection of the dose to be studied for unstable angina was based upon previous experience in the treatment of deep vein thrombosis. Pharmacokinetic and Phase II studies in the early Nineties explored doses in the range of 1 to 2 mg/kg, and the regimen of 1 mg/kg administered subcutaneously twice daily was effective in a Phase III study of DVT treatment which compared enoxaparin to intravenous heparin.

The TIMI 11-A trial in patients with unstable angina explored the tolerability of the higher dose of 1.25 mg/kg, but the rate of major hemorrhage was substantially higher than the

historical heparin control group; whereas, the 1 mg/kg group had a rate of major hemorrhage comparable to heparin. Therefore, the 1 mg/kg dose selected for the ESSENCE trial was validated.

We do not plan to present the TIMI 11-A study in detail here, in order to allow more time for presentation of the ESSENCE results.

In closing, I would like to leave you with the following message. Enoxaparin, which has been extensively used in the treatment of deep vein thrombosis at a dose of 1 mg/kg every 12 hours, has potential advantages over unfractionated heparin in the treatment of patients with arterial thromboses.

The ESSENCE trial was designed to test the hypothesis that these advantages would translate into clinical superiority in patients with acute coronary syndromes.

I would now like to introduce Dr. Marc Cohen, the Steering Committee Chairperson of the ESSENCE trial. He will first discuss the clinical use of anticoagulants in acute coronary syndromes, and then present the ESSENCE results.

DR. COHEN: Dr. Massie, Dr. Talarico, and ladies and gentlemen, members of the panel, it's my privilege to present the primary efficacy analysis for

the ESSENCE study.

The guidelines published by the agency for Health Care Research, Policy Research, the group chaired by Dr. Braunwald focusing on treatment guidelines for unstable angina and non-Q-wave MI, described the role of combining several drugs together in treating patients with these acute coronary syndromes.

In specific, anti-thrombotic agents were recommended to be combined with anti-anginal agents for maximum benefit. In general, these are the current clinical standards that are used throughout the country and throughout the world to combine anti-thrombotic agents such as aspirin and heparin with nitrates, beta blockers and calcium channel blockers.

These guidelines and the current standard of care is based on several previous randomized clinical studies, which show that there is a strong trend in favor of combining unfractionated IV heparin with aspirin over aspirin alone in these patient subsets.

More recently, experience has been gathered regarding the role for low molecular weight heparins in unstable angina. In the recent FRISC study, a large randomized study of roughly 1500

patients, the treatment assignments were to either the low molecular weight heparin dalteparin plus aspirin, versus aspirin alone.

In this particular blinded study, there was a highly significant reduction in the double endpoint of death and MI in favor of the combination anti-thrombotic regimen with low molecular weight heparin and aspirin, as opposed to aspirin alone; and this favorable effect was also seen in the triple endpoint.

A more recent application of low molecular weight heparin, dalteparin, was applied in the FRIC study in which they presented a head to head comparison between dalteparin and aspirin versus standard unfractionated heparin plus aspirin in unstable angina and non-Q-MI. Their study was unblinded in the first phase, and they observed roughly equivalent treatment effects between the two anti-thrombotic regimens.

On the basis of this background, I'd like to describe the ESSENCE study that was developed to evaluate the efficacy and safety of subcutaneous enoxaparin low molecular weight heparin in non-Q-wave coronary events.

The Steering Committee consisted of myself

and several prominent academic cardiologists, and hematologists, and the Clinical Events Committee was charged with adjudicating all of the clinical primary endpoints, death, myocardial infarction, recurrent angina, and also safety endpoints such as major and minor hemorrhage.

The adjudicated endpoints derived from this committee's work were the final status of that patient, and that was what the basis of the statistical analysis that you'll see shortly was about.

The design of the study was randomized, double blind, double dummy, placebo controlled, parallel groups. 3171 patients were enrolled in the study at 176 centers in three continents. Ten countries were involved in this study.

The design was relatively straightforward. Patients with rest unstable angina or non-Q-wave MI were randomized to one of two treatments. The first treatment was with enoxaparin at 1 mg/kg subcutaneous every 12 hours, 1 mg containing about 100 anti-Xa units. In addition, these patients received intravenous unfractionated heparin placebo and aspirin.

The other patients were randomized to

active unfractionated heparin IV, dose adjusted to maintain the APPT to roughly twice control, and they also received a subcutaneous placebo for enoxaparin and aspirin.

Follow-up was conducted at 14 days and at 30 days. The minimum trial drug treatment was for 48 hours, and the maximum up to eight days.

The inclusion criteria focused mostly on patients with rest angina, and they must have had an episode of chest pain within 24 hours of randomization. In addition, there must have been definite evidence of underlying CAD by at least one of the following being present, namely, ECG changes, previous MI or angioplasty, and/or previous angiography documenting at least a 50 percent vessel stenosis.

The exclusion criteria focused mostly on excluding patients in whom the personal physician was planning to revascularize the patient, irrespective of clinical outcome on medical therapy, and also we made every attempt to exclude evolving Q-wave MIs who had persistent ST segment elevation.

The primary objective was very clear cut. That was to demonstrate the superiority of enoxaparin at the dose of 1 mg/kg every 12 hours versus standard

intravenous unfractionated heparin, and to demonstrate this superiority on the composite triple clinical endpoint of death, MI or recurrent angina.

We also sought to demonstrate that this level of treatment with subcutaneous enoxaparin 1 mg/kg was at least as safe as unfractionated heparin.

Based on the available trials published at the time of the design of the ESSENCE study, we projected an event rate for our control group treated with unfractionated heparin of 16.5 percent. In order to appreciate a reduction with the enoxaparin treatment down to 12.4 percent at a power of 90 percent and with an alpha error of about 5 percent, we projected that we would need 1572 patients per treatment group.

The primary analysis performed on the all-randomized population consisted of looking at the triple composite endpoint at 14 days. Secondary analyses were conducted on the triple endpoint at 48 hours and 30 days, and also on the double endpoint of death and MI at 48 hours, 14 days, and 30 days.

The protocol definitions for recurrent angina consist of angina associated with ECG changes or angina prompting urgent revascularization or angina prompting rehospitalization. With regard to

myocardial infarction, this was adjudicated if there was a CK-MB greater than normal and at least three percent of total CK or a total CK greater than twice the upper limit of normal or new or significant Q-waves.

Because of the significant fraction of this population that undergoes revascularization, we also pre-specified our definitions for MI occurring either in the setting of PTCA or in the setting of CABG wherein a patient who had greater than three times an upper limit of normal elevation in CK or CK-MB was described as experiencing a peri-PTCA MI, and patients having CK-MB elevations greater than five times the upper limit of normal were described as having a perioperative MI.

In the perioperative setting, new significant Q-waves could also have qualified the patient for myocardial infarction.

We used a slightly broader definition of death, including patients who were successfully resuscitated from cardiac arrest.

With regard to safety, the major hemorrhages were determined when this was associated with either death, transfusion of at least two units of blood, or a drop in the hemoglobin greater than 30

grams per liter or any retroperitoneal, intraocular or intracranial hemorrhage.

The patient enrollment distribution was basically 30 percent in the United States, 40 percent in Canadian enrollment sites, and roughly 30 percent in South America and in Europe. The baseline characteristics showed good balance.

With regard to several baseline characteristics, we could be a little more specific. There were roughly 30 percent of the population that were female, a large number of the population that were elderly, and close to 60 percent equally distributed between the two groups had ECG changes on admission.

One particular variable that was not evenly distributed between the two treatment groups was the presence of Q-waves, and this was more often found in the enoxaparin treated group than in the heparin treated group. This imbalance in baseline characteristic did not affect the ultimate primary endpoint analysis.

With regard to coronary risk factors, these were evenly distributed between the two treatment groups, and with regard to prior history of aspirin use, you see that at the time roughly 60

percent of both patient populations had aspirin on board. In addition, 20 percent roughly had had prior PTCA, equally distributed between the two groups, as well as coronary bypass surgery.

Ninety-eight percent of all randomized patients received at least one dose of trial drug, and close to 70 to 75 percent received their first dose within 12 hours of their qualifying anginal pain. The median time to treatment was only eight hours. The duration of trial therapy was equal in both groups, with a median time of about 2.6 days, and the mean time of three to 3.2 days.

A very careful blinding system to make sure that the local investigators and health care professionals were not aware of treatment assignment focused around blinding with regard to the aPTT measurements. This system was put into place before any patient could be enrolled at that center.

Basically, the aPTT samples were sent to the local site lab, and the aPTT results were forwarded only to an unblinded professional, and this individual followed the local nomogram to make adjustments in patients randomized to active unfractionated heparin, to maintain them between -- within the range that the local institution had as

their guideline, and in the event the patient was randomized to IV heparin placebo, mock values provided by the sponsor were used to order adjustments in the IV placebo.

This slide is meant to illustrate that our control group was very aggressive and adequately treated. Our patients who were randomized to unfractionated heparin, for the most part, close to 85 percent, had either therapeutic aPTTs or slightly super-therapeutic aPTTs. In other words, only 15 to 18 percent of our control population was subtherapeutic with regard to their aPTT.

In contrast, the recent TIMI 9B study between the time periods of 24-48 hours had roughly 48-52 percent of their patients at a subtherapeutic aPTT level. So our control group, we feel, was very adequately treated.

The most important findings of the ESSENCE study are depicted on this slide. The primary analysis at 14 days showed a significant reduction in the triple composite endpoint from 19.8 percent in the standard unfractionated heparin treated group down to 16 percent in the enoxaparin treated group, with a p value of 0.019.

Of great clinical significance is that

this significant reduction in ischemic events secondary to treatment with enoxaparin was sustained out to 30 days with a relative risk reduction of 15 percent by 30 days.

I would also like to highlight that even as early as 48 hours, a risk reduction in favor of enoxaparin was appreciated of roughly 16 percent.

The Kaplan-Meier curves describing the time to worst event is depicted on this slide, and shows you that the curves begin to diverge as early as two to three days and, importantly, continued to diverge out to 30 days.

The Kaplan-Meier curves for time to first event parallel the previous figure, again showing divergence all the way out to 30 days.

With regard to the more focused definition of recurrent angina as angina requiring or resulting in urgent revascularization, an analysis on the triple composite endpoint using death, MI and recurrent angina prompting revascularization indicates that treatment with enoxaparin results in a very highly significant reduction in ischemic events relative to unfractionated heparin.

The protocol definition of death and MI analyzed out to 14 and 30 days, as well as 48 hours,

shows a highly consistent trend favoring enoxaparin over unfractionated heparin. So from as early a time period as 48 hours, one appreciates a risk reduction of roughly 16-17 percent up to 20 percent. Irrespective of the time point and irrespective of all randomized or all treated, there is a very, very strong trend favoring enoxaparin over unfractionated heparin for the double endpoint of death and MI.

When one uses the more focused definition of death, excluding death that was successfully resuscitated from a cardiac arrest, one appreciates that at 30 days again there's a very strong risk reduction that approaches statistical significance in favor of enoxaparin at 30 days.

A look at the Kaplan-Meier curves describing the time to first double endpoint of either death or MI using protocol definitions, you can see again that, in consistency with the main triple endpoint, there is already the beginning of divergence with reference to the double endpoint as early as two days, and very importantly, these curves continue to diverge out to 30 days.

This odds ratio plot of the effect of pre-specified baseline characteristics relative to treatment shows a very highly consistent trend in

favor of enoxaparin across almost all the pre-specified subsets, the point estimates for almost all the pre-specified subsets lying to the right of the zero bar favoring treatment with enoxaparin.

In specific, I would like to highlight the fact that treatment with enoxaparin is favorable in both genders, male and female. There is a highly beneficial effect of treatment with enoxaparin among elderly patients as well, and in the higher risk subsets of patients with ECG changes or ST depression or prior aspirin users who have failed therapy with aspirin alone, there is a highly significant favorable effect of enoxaparin over unfractionated heparin.

A very important, clinically meaningful additional observation made in our study was that the number of patients who required revascularization who were treated with enoxaparin was significant lower than the number of patients who required revascularization treated with unfractionated heparin. In addition, the total number of diagnostic procedures was also significantly lower in those patients treated with enoxaparin.

Consistent with these findings is the analysis of health care utilization focusing on total ICU days and total hospital days, showing that for the

study as a whole, as well as for the U.S. patients, there is a trend towards lower ICU days and lower total hospital days in those patients treated with enoxaparin relative to unfractionated heparin.

A substudy of 160 patients randomized in Canada used Holter monitoring to detect ST segment changes and myocardial ischemia. Holter monitoring was done for 48 hours during trial therapy, and then repeated 48 hours for 48 hours after termination of trial therapy.

The results again are very consistent with the overall benefit of enoxaparin over heparin. During trial therapy, there was a significant reduction in the number of ischemic events in patients treated with enoxaparin over heparin and, more importantly, after trial drug was discontinued, there was a sustained reduction in the number of ischemic events in patients treated with enoxaparin over unfractionated heparin.

All of the data I just presented to you would suggest the following conclusions. At 14 days the risk of death, MI and recurrent angina is significantly lower in patients assigned to the enoxaparin low molecular weight treatment regimen compared to heparin.

When a more focused definition of recurrent angina prompting revascularization is used, this significant benefit is even greater. Very important from a clinical significance point of view is the fact that this reduction in ischemic events is sustained out to 30 days.

Consistent with these findings on clinical outcome is the fact that resource utilization is reduced in patients that are treated with enoxaparin relative to unfractionated heparin, and this is based on the number of invasive procedures and revascularizations out to 30 days.

Lastly, I would like to emphasize that enoxaparin consistently decreased the incidence of the double endpoint of death and MI at all time points for all populations, with a risk reduction of about 20 percent out to 30 days.

At this point I'd like to invite Dr. Fromell to review the safety and hemorrhage data that we observed in the ESSENCE study.

DR. FROMELL: Good afternoon.

The adverse events that were collected in the ESSENCE study were all serious adverse events, nonserious events that were related to study drug or caused discontinuation of study drug and, of course,

all hemorrhaging. I'm going to concentrate the presentation on the hemorrhage information, since that's the most relevant to safety.

As mentioned by Dr. Cohen, the Clinical Events Committee reviewed all endpoints in a blinded fashion, and for hemorrhages they rendered the determination as major, minor or no event. In addition, the CEC also noted the reason for the classification of the major event and whether or not it occurred in the setting of coronary artery bypass grafting.

This slide shows the definition for major hemorrhage. That was a clinically overt bleed that caused one or more of the following: Death; transfusion of at least two units of pack cells or whole blood; a drop in hemoglobin of 30 grams per liter or more; or was retroperitoneal, intracranial or intraocular in location.

A minor hemorrhage was an overt hemorrhage that did not meet the classification for major and was felt to be notable by the committee. Minor hemorrhages included but weren't limited to epistaxis lasting longer than five minutes or requiring intervention, ecchymosis or hematoma greater than 5 centimeters, macroscopic hematuria unassociated with

urinary trauma, subconjunctival hemorrhage that caused cessation of therapy, or GI hemorrhage, again unassociated with trauma.

Now this slide shows the major hemorrhage rates for both the 30 day period of the trial and the on-treatment period of the trial. As you can see, at 30 days the rate of major hemorrhage was comparable in both groups, being 7 percent in the heparin group and 6.5 percent in the enoxaparin group.

During the on-treatment period, again the major hemorrhage rates were comparable, being 1.2 percent in the heparin group and 1.1 percent in the enoxaparin group.

Now this slide examines the classification categories of major hemorrhage over the 30 day period, and also the causality of the major hemorrhage. As you can see, there was only one death due to hemorrhage, and that was in the heparin group. There were two retroperitoneal hemorrhages, one in each group, and only one intracranial hemorrhage, occurring in the heparin group.

The most common reason to classify a major event was a drop in hemoglobin and/or the need for transfusion of two or more units of blood. Not surprisingly, the most common cause of a major

hemorrhage was surgery or instrumentation, and the most common type of surgery and instrumentation was coronary bypass grafting.

Now this slide displays similar data to the last slide, but it shows the major hemorrhage rates on treatment. As you can see, there were no deaths during the on-treatment period or intracranial hemorrhages. There was only one retroperitoneal bleed. That occurred in the enoxaparin group.

Again consistent with the previous slide, the most common reason for categorizing an event as major was a drop in hemoglobin and/or the need for transfusion. Also consistent with the last slide, the most common cause of a major hemorrhage was surgery instrumentation, though during the on-treatment period coronary artery bypass grafting did not contribute to this. Rather, it was angiography and/or PTCA.

Now although the major hemorrhage rates were comparable in both groups over 30 days or the on-treatment period, when one analyzes major and minor hemorrhages together, there was a significantly higher rate of hemorrhage in the enoxaparin group.

Now this slide breaks out the all-hemorrhage rate into major hemorrhage and those patients that had only minor hemorrhage. As you can

see, the rate of minor hemorrhage was 7.2 percent in the heparin group and 11.9 percent in the enoxaparin group, a highly significant finding, with a p of less than .001.

Now despite this higher rate of minor hemorrhage in the enoxaparin group, minor hemorrhages rarely resulted in any action by the investigator in either group. They led to discontinuation of study drug in less than two percent in each group. They required a transfusion in half a percent or less in both groups, and they were deemed serious again in only half a percent or less in both groups.

When one looks at the various categories of minor hemorrhage, the reasons for the significant increase in the rate of minor hemorrhage in the enoxaparin group becomes apparent. Now this slide displays the various categories of minor hemorrhage, and I should point out that these categories are not mutually exclusive. Patients can be represented in more than one category.

So looking at the enoxaparin bar on the right, as you can see, injection site ecchymosis or hematoma, which is medication injection site, makes up the largest category of minor hemorrhage, followed by sheath hematoma. The remaining categories combined

are otherwise comparable in both groups.

So based on the results I presented, one can conclude that the rate of major hemorrhage events associated with enoxaparin treatment versus heparin treatment in patients with unstable angina and non-Q-wave MI is comparable.

There is a higher rate of overall hemorrhage events due to minor events that's associated to enoxaparin therapy in this patient population, and that's due to angiography, sheath side, or medication injection site hematoma ecchymosis.

That concludes my presentation. I'd like to now introduce Dr. Eugene Braunwald. Dr. Braunwald was the Chairman of the committee that developed the clinical practice guidelines that you heard about earlier in the presentation, and he'll comment on the results of the ESSENCE study in context with other trials, and the impact on patient care.

DR. BRAUNWALD: Dr. Massie, members of the Advisory Committee, I've been asked to comment on the clinical impact of the ESSENCE trial.

Since unstable angina is a very common condition which accounts for a significant amount of disability and death, a therapeutic advance is likely

to have an important impact on patient care. In recent years, therefore, the search for better therapies for the acute coronary syndromes has become intense.

Although there have been notable disappointments, there have also been remarkable successes, such as thrombolytics and anti-platelet agents. At the core therapy for unstable angina and non-Q-wave myocardial infarction are the complementary contributions of an anti-platelet agent and an anti-coagulant, the most basic of which have been aspirin and intravenous unfractionated heparin, until now.

This combination has come into wide acceptance since the original publication by Pierre Theroux and his colleagues in 1988. The unstable angina clinical practice guideline published in 1994 was developed by a private sector panel convened by the Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute.

A detailed review of the available literature at that time led to the recommendation that "intravenous heparin should be started as soon as a diagnosis of intermediate or high risk unstable angina is made."

The strength of evidence for this was

classified as: (a) indicating that the evidence for the recommendation was strong with at least one randomized controlled trial as part of a body of literature of overall good quality and consistency. Applying these criteria to the current situation, it seems time to revise these guidelines to include subcutaneous low molecular weight heparin.

I think the ESSENCE trial was a well designed trial incorporating all of the elements we have come to demand of a trial whose conclusions are meant to result in a change in clinical practice, such as careful blinding, blinded evaluation of clinical events and hemorrhage, and independent statistical analysis.

I understand that the paper that describes this trial has just been accepted for publication in the New England Journal of Medicine.

In addition to the strength of the primary endpoint, what has impressed me as I review the study data is the consistency of the results. It's always reassuring to see consistency within a trial, because it lends credence to the overall conclusions.

In the ESSENCE trial we find consistency, no matter how the endpoint is defined, consistency among the time points examined, consistency within

subpopulations. This is really all the more remarkable when we remind ourselves that this is a trial against an active comparator drug, and an active comparator that has achieved widespread acceptance in clinical practice, unfractionated heparin.

The efficacy of enoxaparin over heparin has been clearly demonstrated in the ESSENCE trial with safety equivalent to intravenous heparin. In addition to efficacy and safety, subcutaneous enoxaparin seems to have additional advantages relevant to today's cost conscious environment. With no need for an intravenous line of blood sampling to monitor anticoagulant effect, use of enoxaparin is advantageous for the physician, for the nurse, and most of all, for the patient.

All of the measures of resource utilization seem to indicate that this is one of those unusual situations where we will be able to achieve better efficacy with less utilization of health care resources.

So the ESSENCE trial, I believe, met its primary objectives, and additional effects lend support to the primary endpoint. When a double endpoint of death plus MI is considered, the real hard endpoints, the risk reduction was nearly 20 percent,

which is certainly clinically meaningful.

The data are internally consistent and statistically robust.

In summary, what you've seen today is a consistent picture of a drug which, I believe, should now be added to the cardiologist's therapeutic armamentarium for the treatment of unstable angina.

I'll turn the discussion over to Dr. Rush.

DR. RUSH: Dr. Massie and members of the panel, and ladies and gentlemen, in the questions prepared for the consideration of the committee today, FDA asks the committee to consider the ESSENCE trial in light of the draft guidance document reviewed by Dr. Talbott at the beginning of this presentation.

In order to assist the committee in this task, we would like to review several key elements of the ESSENCE study as they relate to the guidance document. There are several points in the guidance document which are specifically relevant to the use of a single trial as the basis of approval.

The trial must be a large multi-center study. There might be multiple studies within this single study. Multiple different endpoints might support the efficacy of the drug, and the statistical result should be very powerful.

In a large, well designed study, the results should not be driven by any one site or country. In the ESSENCE trial, the largest site contributed only 6.8 percent of the total enrollment. Canada enrolled the largest number of patients with 40 percent of the total, and the U.S. was the second largest enroller with 30 percent.

With respect to the observed effects on the primary triple endpoint, country adjusted odds ratios do not differ from unadjusted odds ratios.

Consistent with other aspects of a well designed study, baseline imbalances were rare and had no effect on the primary endpoint. Unblinding was also rare. There were no post hoc changes in the primary endpoint analysis.

The only change to the planned analysis was the change from the original objective of equivalence to a superiority objective. This change was made very early in the study at the request of FDA, occurred well prior to the performance of the interim analysis.

In a well designed study, the major results must reflect the primary hypothesis prestated in the protocol. In the case of the ESSENCE study, the 14 day incidence of the triple endpoint was

reduced by 16.2 percent, significant at a p value of 0.019 and sustained through 30 days. The results are entirely consistent, considering either the all randomized or the all treated patient population.

The ESSENCE trial was not powered to show independent significance in subpopulations of the trial. However, it is of interest that the U.S. subset of patients demonstrated a 20 percent risk reduction in death, MI and recurrent angina at 14 and 30 days, which in a statistical sense was a strong trend at 14 days and statistically significant at 30 days.

The U.S. patients demonstrated approximately a 40 percent risk reduction in death and MI, statistically significant at 14 days, and a strong trend at 30 days.

Two important additional pieces of data separate from the main endpoint results are supportive of the efficacy of enoxaparin. First is the reduction of revascularizations and procedures in the enoxaparin group. The reduction in PTCAs in the 30 days following administration of study drug was highly significant. Diagnostic coronary artery catheterizations were significantly reduced.

This is a clear indication that the study

drug was influencing patient management in a clinically meaningful way.

A second, completely independent evaluation of drug efficacy is provided by the subset of patients who wore 48 hour Holter monitors. The reduction in transient SD depression is an independent measure of the efficacy of enoxaparin in preventing ischemic events.

There were significantly fewer transient ischemic episodes in the enoxaparin group, both in the first 48 hours and in the 48 hours following discontinuation of study therapy.

The protocol specified primary endpoint gave a statistically robust result. However, many recent studies have used a more focused definition; that is, recurrent angina prompting revascularization. Using this definition, the relative risk reduction is 23 percent, with a p value of 0.004.

In the past, a single trial has been the basis of approval when the study drug had demonstrated a clinically meaningful effect on death and irreversible morbidity. This is the Kaplan-Meier curve of the time to death and MI.

The curves show a clear divergence which continues over the 30 day period and represents a 20

percent risk reduction. For true death and MI, the difference yields a p value of 0.054.

This p value, certainly impressive for a trial not powered to demonstrate an effect on death and MI, would have been quite strong if it had been possible to study enoxaparin plus aspirin against aspirin alone.

This was not possible, due to the widespread clinical use of heparin in unstable angina. However, at the request of FDA we performed an additional analysis to evaluate the impact of an active control on the magnitude and statistical significance of the enoxaparin effect observed in the ESSENCE trial, taking into account the published literature data on the effect of heparin plus aspirin on death and MI.

In this analysis we attempted to evaluate what would have been the true statistical significance of these results, had the enoxaparin plus aspirin regimen been compared to aspirin alone rather than to an active control. To do so, we combined the ESSENCE data with the results of the meta analysis published by Oler, et al., comparing heparin plus aspirin to aspirin alone. This was the meta analysis shown to you earlier by Dr. Cohen.

The question was addressed through two complementary approaches, both providing consistent results. This documentation was sent to the Committee on June 23. If the Committee would like to see additional slides, data slides are available.

The conclusions of the analyses are that, if the ESSENCE control arm had been aspirin alone, the odds ratio of enoxaparin plus aspirin versus aspirin alone for death plus MI would have been .58, resulting in a p value of .02.

Furthermore, from the ESSENCE trial it can be determined that the probability for enoxaparin plus aspirin to be truly superior to heparin plus aspirin is in the range of 92 to 95 percent for death and MI.

There are other considerations to be applied when considering a single multi-center study as the basis of approval. The first two of these, internal consistency and pharmacologic rationale, I will address in a moment.

Regarding the third bullet, we can consider the results of the FRISC trial with dalteparin, which demonstrated a clear benefit of dalteparin plus aspirin over aspirin alone, and RPR is not aware of any data which would contradict the conclusions of the ESSENCE trial.

Let's return now to the first bullet, internal consistency. Internal consistency is an important consideration in the FDA draft guidance document and is one of the strongest points of the ESSENCE trial. This slide emphasizes the consistency across subgroups.

I know it cannot be seen clearly on this slide, but the information is reproduced on page 39 of the sponsor briefing document. In 50 subpopulations examined, enoxaparin was favored over heparin in nearly every subpopulation. The point estimate favored heparin in only two subgroups, and both of these were small subgroups with wide confidence intervals. The overwhelming impact of the picture is that enoxaparin was favored in most subpopulations.

There is also strong consistency among the components of the triple endpoint. Odds ratio reductions are directionally consistent and similar in magnitude for recurrent angina and MI at all time points and for death at 30 days.

Even though the ESSENCE trial met its pre-specified primary objective, could it be that redefining the triple endpoint in a different way would have produced a different conclusion?

The blinded Clinical Events Committee

categorized the endpoints in such a way that it is possible to examine alternative definitions of the pre-specified endpoint, and as this table shows, the odds ratio is either maintained or gets stronger when alternative definitions are utilized.

There are a number of mechanisms which can explain why low molecular weight heparins might be superior to unfractionated heparin. In trial after trial, it has been shown that intravenous heparin is a very difficult drug to use. Enoxaparin, by contrast, results in reliable anticoagulation.

That, in itself might be a sufficient explanation for the ESSENCE results, but probably other factors are important as well. In the platelet rich environment of an arterial thrombus, the resistance of enoxaparin to the inactivation by platelet factor IV might be of critical importance, and since the inability of the direct thrombin inhibitors to demonstrate superiority over heparin in acute coronary syndromes, we have believed it's vitally important to inhibit thrombin generation, which inhibitors of Xa are able to do.

The draft guidance document mentions that a single trial which satisfies one or more of these conditions may be adequate as the basis of approval.

In the case of the ESSENCE trial, we believe that the majority of the points raised in the FDA draft guidance document are favorably addressed.

This concludes our presentation, and we would be pleased to take the Committee's questions.

CHAIRMAN MASSIE: Thank you very much. I guess the question -- and it probably is going to come up again -- You mentioned some more slides. Without getting too overwhelmingly didactic about the imputed placebo, have you got something that can carry us through that a little bit without taking too long, I guess it would be worth showing it to us.

DR. DURRLEMAN: Good afternoon. I am Sylvain Durrleman from Biostatistics.

What we have tried to do is to evaluate what would be the strength of evidence of the ESSENCE trial if we had used aspirin arm instead of heparin plus aspirin. So several items have been published and we tried here to do so, and what we have used here is an approach which was proposed by Dr. Temple a few years ago and, subsequently, published by Tom Fleming, a prominent statistician in the context of the AIDS clinical trial.

What we have used here is the effect of heparin plus aspirin as opposed to aspirin alone on

the double endpoint of death and MI, as published in the literature in the meta analysis that Dr. Cohen referred to earlier.

In that particular article, which is the largest body of evidence of the efficacy of heparin with aspirin, the odds ratio which was obtained was .67 with a confidence interval just exceeding 1. I think it was 1.02, so suggests a trend efficacy of heparin plus aspirin to reduce the incidence of death and MI by about 33 percent.

The next confidence interval you have here relates to the odds ratio of enoxaparin plus aspirin versus heparin plus aspirin such as derived from the ESSENCE trial. So for the double endpoint of death and MI, we obtained 22 percent reduction in the incidence of death and MI with a p value of .08.

So the goal was then to try to identify what would be the odds ratio of the comparison between enoxaparin plus aspirin versus aspirin alone. It turns out that in the metrics of odds ratio, really the original odds ratio is a simple product of the odds ratio of the effect of heparin plus aspirin, then multiplied by the effect -- the additional effect of enoxaparin plus aspirin.

We can easily derive the confidence

interval around those estimates, and we will reach an odds ratio of .58 with a confidence interval which is from .36 to .92. So a sizeable reduction which is estimated to be about 42 percent in the reduction of death and MI, if we had compared enoxaparin plus aspirin versus aspirin alone.

So this is a standard, reasonable approach to try to factor in the published literature in interpreting -- Subsequently, we also have looked at different abstracts which could hopefully corroborate those findings.

Particularly, in the active controlled trials, one of the implicit objectives is to determine whether the experimental drug is effective relative to the placebo or, in our case, to aspirin alone. In addition to that, another objective is to estimate the magnitude of the effect of enoxaparin plus aspirin relative to aspirin. That's just the effect of heparin plus aspirin relative to aspirin.

It is very clear from those two implicit objectives that, to do so properly, we need to explicitly use the prior information about the outcome of trials which have compared heparin plus aspirin to heparin in the past. It leads very naturally to different statistical methods which is based on

Bayesian concepts.

Next slide, please. So we adapted a methodology which was proposed by Richard Simon at NCI in the context of cancer clinical trials recently, using a simple model for the positive control trial analysis. What we tried to do here is to model the odds with a very simple linear model having three parameters and two indicator variables for the treatment codes, and just an experimental role.

Next slide, please. The specification of the indicator variables zero and one for treatment groups are such that --

CHAIRMAN MASSIE: I think you're losing us here.

DR. DURRLEMAN; Oh, I'm sorry.

DR. MOYE: I'm having a great time over here.

CHAIRMAN MASSIE: Are you having a good time?

DR. MOYE: I'm enjoying this, but it's okay.

CHAIRMAN MASSIE: Will you be able to explain it to us?

DR. DURRLEMAN; I think just a point -- It's not too complicated. We can go to the next

slide.

CHAIRMAN MASSIE: To give us the bottom line, I guess, okay.

DR. DURRLEMAN: I apologize for this.

What we have done vertically is to use the prior information about the effect of heparin plus aspirin versus aspirin, according to three possible hypotheses. One would be taking the meta analysis published at face value; that is, assuming a -- or not threshold -- So you have a relative risk of .67 with a confidence interval of .44 to 1.02, and this gives us about the distribution.

Now it's reasonable to assume that meta analysis are -- So we have also used more skeptical -- with a risk prediction of only 20 percent or even 10 percent, assuming a very marginal effect of heparin plus aspirin.

So let's see the next slide. Next slide, please. So based on this model, we can easily derive as a probability of some hypothesis of interest. Some of this hypothesis was the one which was asked to us by the FDA: What would have been the strength of evidence if we had to compare ourselves to aspirin, and this is particularly shown in this first column where you have for values prior hypothesis as to

effect of heparin plus aspirin, the corresponding probabilities.

In this row here you have the hypothesis concerning the meta analysis effect. Here we have a more skeptical view of the data, and here a very skeptical view of the data with very limited effect of heparin plus aspirin.

You can see that, in the first column, the probabilities of Lovenox plus aspirin, the -- of aspirin in any case is very, very small.

We can also derive from those data as a probability that Lovenox plus aspirin will be superior to heparin plus aspirin, and you can see also that whatever the hypothesized effect of heparin plus aspirin, the probability is very high, in the range of 90-95 percent.

The Committee also asked us to review what would be the probabilities that Lovenox plus aspirin maintains at least 50 percent of the effect of heparin plus aspirin, and you can find those data in this column here, and you can see that in the more skeptical view, it will be 93 percent up to 99 percent.

Actually, the good news is that we can really guaranty up to 90 percent confidence that 100

percent of the effect of heparin would be -- and that it's very likely also that we would exceed that. Thank you.

CHAIRMAN MASSIE: Well, thank you very much. I'm not sure I expected such a torrent of data, but I think that, in fact, we all know that in the future we're going to be seeing more and more of these active comparator trials, and we might as well get used to determining how to think about them.

I guess we should ask -- When we talked about skeptical, then next we'll ask our committee skeptic to tell us what he thinks of these analyses.

DR. MOYE: I would say this. I think that the type of Bayesian analysis you've seen here is very disciplined. It is very -- provides a very clear statement of the possible additive effect that the intervention drug that we are considering today may have over aspirin.

I am very much concerned, though, on the sensitivity of the results that we saw just a moment ago to the underlying efficacy data that comes from this trial. Now let me go on to say that the efficacy data from this trial is critically dependent on the ascertainment of vital status for patients. In fact, that's true for any study. That's a truism.

if I could give the specifics here, there are -- The p value that is provided for the primary endpoint is a 0.019, and that was very easy for me to reproduce. However, there are 14 patients by my understanding -- and if I'm wrong, please tell me I'm wrong -- but by my reading there were 14 patients who had unknown vital status at the end of the trial.

Now in order to come up with that p value of 0.019, we have to make certain assumptions about those patients with unknown vital status. The investigators have made some assumptions, but they are not the only assumptions.

An alternative assumption would be as follows: Of the 14 patients, eight of them were randomized to Lovenox. If I assume that those eight patients, in fact, are dead, the p value is no longer 0.019. It is, by my back of the envelope computation, 0.049.

The threshold that the investigators have identified for significance is 0.048. Now I am not -- it is not my intent to spark a debate about the third decimal place of a p value. My intention is only to point out the very sensitive nature of the efficacy findings with regard to assumptions about vital status.

CHAIRMAN MASSIE: Well, thank you. is that correct that those people -- their vital status still remains unknown?

DR. RUSH: At the time that the application was filed, there were some patients lost to follow-up, which we have been able to trace further. The assumption made in the analysis was that none of the patients lost to follow-up had had endpoints.

What you see on this slide is that we were able to contact 26 patients in the heparin group, 25 in the enoxaparin group, confirm that there was no endpoint in 17 of those, confirmed that -- 17 in each group -- confirmed that others were alive, 9 and 8. So that most of the patients that were lost to follow-up in the information you've received have been found, and we've confirmed that they have no endpoints, and we're left then with eight in the heparin group and 14 in the enoxaparin group that are truly lost to us as of now.

DR. MOYE: I'm sorry. Can you -- Let me just ask you directly. At this point, how many patients in the Lovenox group had unknown vital status at day 14?

DR. RUSH: At day 14? I'm sorry.

DR. MOYE: Which is when the endpoint -- but the endpoint measurement is at day 14. Now, of course, if they are alive at -- Well, if they're alive at day 30, then they're alive at day 14.

CHAIRMAN MASSIE: Let's go on with the discussion, and you can come back if you have that information. Marv, you want to lead off?

DR. KONSTAM: Thanks, Barry. The first question I have relates to the anti-thrombotic effect. I guess it's reasonable to guess that the differences that you see, both in terms of efficacy and in terms of hemorrhagic effects, could be mediated through a greater anticoagulant effect in the enoxaparin group versus the unfractionated heparin.

What can you tell us about that vis a vis anti-Factor Xa effect or anything in the two treatment groups?

DR. COHEN: My response would basically be a reiteration of some of the data you saw derived from the TIMI 11A study where --

DR. KONSTAM: I mean in this study.

DR. COHEN: Well, our substudies performed in Argentina and a substudy performed in Canada on Factor Xa or, I should say, Factor anti-Xa activity parallels exactly the experience in the TIMI 11A

group. That is that in the Argentinean substudy and in the Quebec substudy, the median trough values for patients treated with Lovenox was about 0.5 and, as you know, the median or mean peak values with unfractionated heparin are in the range of .3 to .6.

So that in the ESSENCE study, based on substudy information derived from two different continents, the effect on anti-Xa activity was quite consistent with the median level pegged at about .5 at the trough.

DR. KONSTAM: So you're construing that the anti-Xa effect in the enoxaparin group is likely to be more effective than for unfractionated heparin?

DR. COHEN: Yes. There is more anti-Xa activity in the Lovenox group than in the unfractionated heparin group. Now --

DR. KONSTAM; I just wanted to point that out. I mean -- so that it's likely that the effects that we're seeing on both sides of the equation, the effect and -- the benefit and the adverse effects, although not severe, are mediated by the more effective anticoagulation, if you will.

DR. COHEN: Yes.

DR. KONSTAM: Okay. I understand that there was a difference in the two groups in the

duration of treatment as it turned, and particularly the analysis that I saw reflected a cut point of greater than or equal to three days of treatment. That turned out to be different between the two groups.

Could you share that with us again, and give us your analysis of that?

DR. COHEN: What I could do is highlight the fact that the treatment duration, to some extent, obviously, is affected by treatment effect. Therefore, if a drug is less active, there are more likely to be primary endpoints and more likely to be earlier termination of trial therapy.

So the first thing that I would suggest is that we have to be concerned to make sure that we don't talk about a tautology, and that is focus on one time duration of treatment; because, frankly, there were more events in the heparin group in the early time period than there were in the Lovenox group, and that, in and of itself, would terminate trial therapy.

So if one drug is more efficacious than another, de facto, that would trigger an imbalance a little bit in the duration. Keep in mind that, there were some patients that had subcutaneous drug continued longer than the unfractionated intravenous

active or intravenous placebo drug, but those patients were maintained in a blinded status. Half of them received subcu. placebo; half of them received subcu. enoxaparin.

DR. KONSTAM: Well, maybe we could ask the agency. I don't know if Dr. Talarico wants to comment on this. I know that you've focused in on this question in your analyses, and I just wonder if you could comment on it; because I think your points are -- There is a maldistribution in the number of patients treated for more than three days, and your point is well taken that part of that is likely to be related to endpoint differences; but part of it isn't.

As I understand it, based on your analysis, Dr. Talarico, that the p value grows a little bit, if you take that into account.

DR. TALARICO: I think that in the different treatment we also have to take into account that Lovenox would act for much longer periods of time compared to the discontinuation of heparin infusion.

In other words, if we -- After a dose of subcu. Lovenox, the effect might be continued for three, six hours. Stopping an infusion of heparin, the effect after an hour, an hour and a half. So this will have to be taken into consideration analyzing the

treatment.

DR. KONSTAM: Well, I'm just trying to get at whether you feel that -- you know, maybe the sponsor can comment, too -- whether this difference that turned out, you know, is accounted for on the basis of different numbers of events, and that was the cause of the withdrawal -- you know, of the relatively shorter period of time for which the heparin patients were treated, and what do we do with that; because it's a difference in duration of treatment, you know, with the two. Maybe you'd like to comment.

DR. DURRLEMAN: It is difficult to answer directly this question, because, you know, the duration of treatment is a post randomization covariant. So it's difficult to address the analysis on that. It would be improper. However, what we have done is to look at the reduction in events at 48 hours.

So after only two days, you have already a substantial reduction in the rate of events. So this leads us to believe that -- We have also looked at some subgroups in which the duration of treatment was the same for heparin and enoxaparin, and it was pointed out in the review of the FDA, in USA the treatment duration was about the same for heparin and

for enoxaparin, and in this particular country we still found very strong effect of enoxaparin versus heparin.

So we believe that this reassures about this possible imbalance.

What we have done also, although the analysis is not perfect, is we have looked at the duration of the event rate by treatment duration for patients who did not have an event of treatment. Even in patients treated up to two days, there is still a trend in favor of enoxaparin. Granted, it's not a very clean analysis, but I think it's this type of situation where we try to explain with some post hoc, post randomization covariate. It was the best we could do.

DR. KONSTAM: Okay. Let me ask this question. One of the arguments favoring acceptability of the single trial might be that there is other supportive stuff in the literature that makes us believe the result, such as other unfractionated heparins, particularly dalteparin in the first trial.

What can you tell us about the relative anti-thrombotic profile of these two preparations?

DR. COHEN: With regard to dalteparin, focusing simply on the biological activity, you do

have slightly different Xa to IIa ratios. Dalteparin's ratio is slightly more in favor of anti-IIa activity. Enoxaparin, the ratio is basically three to one, favoring more the factor anti-Xa activity.

This actually is a little bit of interesting issue, because in the FRIC study where there was, more or less, equivalence between dalteparin and unfractionated heparin, measurement of the anti-Xa activity revealed that their trough values were on the order of roughly 0.3. In the ESSENCE study, as I mentioned to you earlier in response to your earlier question, there was a heightened anti-Xa effect with enoxaparin relative to dalteparin.

In addition, enoxaparin has a longer duration of biological activity. In some publications in thrombosis and hemostasis where comparisons are made directly between one low molecular weight heparin and the other low molecular weight heparin, the duration of TFPI, the amount of TFPI released, and also the duration of anti-Xa activity is longer with enoxaparin relative to dalteparin.

The most important row there -- you see the second row, the area under the curve for activity, you see, is much higher with enoxaparin at 0.98

relative to dalteparin which is 0.50 at, roughly speaking, similar anti-IIa activity levels.

So there is what appears to be a longer duration of anti-thrombotic activity and maybe even a heightened intensity of anti-thrombotic activity with this particular enoxaparin low molecular weight heparin relative to dalteparin.

I will remind you, however, that in the first study there was quite a robust benefit of dalteparin in concert with aspirin over aspirin alone. So I think that, in general, you know, the low molecular weight heparin and aspirin combination is a good one.

DR. KONSTAM: Okay. Just one last comment, and then I'll turn the microphone to someone else.

The higher incidence of what are called non-severe hemorrhagic events -- you know, I'm guessing, is -- A lot of them are related to caths, you mentioned, and I'm guessing that that has something to do with the fact that, when somebody is on unfractionated heparin, you often stop the heparin for a couple of hours before the cath; whereas, you can't do that with enoxaparin.

So that -- and this is part of the same

point that you're making about the duration of anticoagulant effect. Can you just comment on that, and if we were to approve the drug, you know, what, if anything, should be said about that in the labeling? What kind of advice would you give the clinician about this issue?

DR. FROMELL: We tried our best, actually, to deal with that issue in the ESSENCE trial, because, obviously, it would be a concern for us. As you saw, we had about a third of the patients get revascularized.

What we did is looked at the pharmacokinetics of the drug. We had no actual, you know, trial experience to recommend it, and suggested that we try not to pull the sheath within the first six to eight hours of the last subcutaneous injection, hoping that that would reduce the major bleed rates or bleed rates around the sheath site.

We have an ongoing trial in PTCA using similar sort of criteria, and we'll have actual clinical data relating time course from last subcutaneous dose to sheath pull that will help define that better. As far as the ESSENCE trial, obviously, we can't pull that data out of there.

DR. KONSTAM: Okay.

CHAIRMAN MASSIE: We're going to just go for another ten minutes or so and then take a break.

I wonder, Cindy, you want to ask any questions? Do you have any?

DR. GRINES: Well, I think the data are rather impressive, actually, considering that, although these are called unstable angina patients, in fact they are probably pretty stable, because the investigator had to say up front that they weren't planning to take the patient to the cath lab. I would think that most high risk, unstable angina patients, the operators would not be willing to do that.

I have several questions, one of which is what is the recommended duration of therapy? Again, there -- I guess I couldn't figure out that there was any differences in the duration as measured by the median or the mean, but if you're allowing a range of treatment between 48 hours and eight days, what would be recommended, and is there any analysis based on the duration of therapy?

DR. RUSH: What you're hearing in terms of the 48 hours to eight days is purely what was recommended in the protocol, and we did get that kind of a range in the protocol. Obviously, there are places where revascularization is not available

readily, and those patients could be continued longer, and the patients that went to revascularization earlier went earlier.

So we think that what's been done in this trial is pretty representative of practice under a lot of situations, and that's the recommendation that we would make.

DR. GRINES: But you continue to see a late benefit in patients who were treated out to eight days? So the benefit doesn't -- It's not just an immediate benefit. It's a sustained benefit, if we choose to?

DR. RUSH: Well, I think the sustained benefit of 30 days you achieve with a mean duration of 2.6 days of therapy. So we don't -- Because not that many patients went out to eight days, we can't comment now on any benefit that you would have by continuing it longer.

DR. GRINES: Do you have any data on rebound hypercoagulable states in the unfractionated heparin arm?

DR. RUSH: We were not able to demonstrate rebound clinical events in this trial, which is consistent with what we've heard, that you don't usually see clinical rebound in patients when they're

on aspirin. At least that was true in the Theroux study.

Aspirin blunted the clinical rebound after stopping heparin, but I think the Holter study, although it's very small, gives interesting information that there may be less rebound in the enoxaparin group; but we could not see it in terms of clinical event.

DR. GRINES: So you don't think the big increase in events after the first 48 hours is due to rebound in either group? There is a steady increase in events, even after the heparin was off.

DR. COHEN: I think that the curves you see in the Kaplan-Meier curves here are remarkably similar to the curves you saw, for example, in the GUSTO II study where heparin was also unfractionated. Heparin was the control group, and in neither study was there any sudden rebound after terminating heparin.

Our suspicion is that we're still treating these patients with anti-thrombotic agents, namely, aspirin, and a fair number of these patients are also going on to revascularization. So that in our study and in the GUSTO II study, we didn't really appreciate any dramatic clinical rebound.

I would just highlight again that the Holter substudy with 160 patients is quite intriguing in the sense that it does show that there is a certain number of patients that continue to experience ST segment changes, but that number is quite reduced in the enoxaparin treated group relative to the unfractionated treated group.

CHAIRMAN MASSIE: But in that regard, though, compared to the time during therapy -- I mean, the rebound would show up -- Not comparing the two groups, but what about the people who had heparin withdrawn, and you had Holters before and afterwards.

DR. COHEN: If you remember the numbers in the enoxaparin treated group, the ST segment, the incidence of those two segment changes was roughly like 17 to 18 percent during therapy, and that moved to 22-23 percent, which isn't very dramatic. On the heparin side, it was roughly like 40 percent, going up to 50 percent or something in that range.

I would just have you go back to the curves that were depicted in The New England Journal article describing the GUSTO II data where there was no sudden jump in clinical events with rebound. I suspect it relates to the fact that we're still treating these patients, although not with heparin.

DR. GRINES: Yeah, but in thrombolytic trials you're -- One of the major endpoints is death, whereas in this trial the big endpoint is ischemia or reinfarction, and the curves do tend to separate after the therapy is stopped. It makes me wonder, even if you don't see a discernible increase in events, whether that continued climb in the heparin arm is due to a rebound effect.

I have a question about definitions. Specifically, I was a little confused about the slides that said that these were all protocol defined endpoints, and yet the materials that were provided to us indicated that the events committee had changed all the definitions.

So which definitions were used in this analysis?

DR. COHEN: We, actually -- While my colleagues get prepared to maybe show some of the charter data -- you want to do that?

CHAIRMAN MASSIE: Why don't you try to explain?

DR. FROMELL: There are some slides, if we need to show them; but, basically, the protocol and the protocol definitions were all completed well before we had gotten together the clinical events

committee. So it was indeed when they sat down to clarify and sort of make the definitions a little more specific.

The only definition that was altered that was existing in the protocol already was the definition after CABG that required two of three of the criteria to have an MI, where the clinical events committee felt that anyone of those three criteria were quite adequate. That would be the enzyme elevation greater than five times above normal and development of a new Q-wave or development of new wall motion abnormality on imaging study.

DR. GRINES: Well, we have a whole page of definitions, and they were changed for the reinfarction. Seems to be much more --

DR. FROMELL: There were some clarifications made. That was the only change in the protocol defined definitions. Other clarifications that were made that were important, obviously, was the fact that the investigators did not have the definition of what was an index event, and what was an endpoint to be analyzed. In other words, when was it an entry MI, and when was it an endpoint MI?

The committee did clarify that and used a time point of 16 hours as cutoff. Index events

occurred within zero to 16 hours of study enrollment. Endpoints occurred after 16 hours.

It wasn't made known to the sites. The hope was to engender reporting of events, and then allowing the committee to do away with the variability of deciding the time point.

They also added the additional elements of reinfarction for patients entering the trial with recent MI, since that's a difficult call due to the already abnormal enzymes. That definition included the reinfarction within 16 hours that relied on clinical findings of severe chest pain and ischemic EKG changes, and the chest pain and/or the EKG changes needed to persist longer than 30 minutes for that diagnosis to occur; and then reinfarction after 16 hours relied on enzymes again.

It was a big more complex, but they were designed to create cutoffs in a setting where there were already preexisting enzyme elevations. So that, obviously, was not in the protocol, and it's a shortcoming of the protocol.

DR. GRINES: Well, I think it was in -- Well, at least what was provided to us, there was definitions based on enzyme elevations and 50 percent over the last nadir, and I was curious why it was

changed and how it affected the outcomes.

DR. RUSH: It wasn't really changed. It was something that was not specified completely in the protocol in terms of the definition, but I think what you're referring to is the different referring angina definitions as well, that you see that whole list.

DR. GRINES: Yes. Well, that's pretty clear. It's just that the enzyme definition seems -- Seems like we're diagnosing more MIs with the events committee compared to what the operators --

DR. FROMELL: Right. That, actually, was a function of -- The committee talked with a lot of consultants and quite heavily with both the TIMI group and the GUSTO group, as they were also designing, obviously, large trials and trying to define this very difficult issue.

So the definitions that were actually finally used were a sort of a condensation of those definitions used by both those study groups.

DR. GRINES: And how did it affect the outcome of the trial comparing what the investigators reported versus what the events committee?

DR. FROMELL: Actually, I have some slides to show you on that in a moment.

CHAIRMAN MASSIE: When did the final

decision as to how they were going to define these get made during the course of the study? Was it before they had any endpoints to classify?

DR. FROMELL: Yes. Actually, the charter took a while to be finalized. The endpoint definitions were finalized before they adjudicated events, and what they did, they sat down as a group on telephone and reviewed 15 events, roughly, together to test out the definitions, but also to test out their adjudication form, which also went through a minor revision.

So they did work through the definitions together, finalize them before they started looking at events, then looked at events, testing it, and that's basically how they came to their final decision.

Can you put on carousel 4, slide 3, please?

This is referable to your question about the difference between the endpoints adjudication and the investigators' adjudication. Thank you for your patience.

The top part of the slide here is the 14 day mark, and the bottom part is the 30 day mark, and we've displayed here both the triple and double endpoints. As you can see, for the triple endpoint

the -- this is all investigator driven now. The triple endpoint is much higher significant level for the triple endpoint at 14 days, and a similar sort of significance for the triple endpoint at 30 days.

The double endpoint, however, does not show the same reduction in death and MI either at 14 days or 30 days.

Now I should also highlight that this sort of finding with the clinical events committee is not necessarily new. Clinical events committees are used, as you know, pretty standardly in cardiovascular trials, and the effect of the committee disagreeing with the investigator is not uncommon.

DR. GRINES: Well, it's not uncommon, but has it been shown to make a difference in predicting mortality and hard endpoints?

DR. FROMELL: The short answer is yes, and the little bit longer answer is three slides, if I can show them. There are three studies where the clinical events committee results are shown.

Okay. The first study will be the recent GUSTO IIb trial which, as you know, was a 12,000 patient trial. 8,000 patients within this trial had non-ST elevation, which corresponds to unstable angina non-Q.

In the top part of the slide, you see the site adjudication, the investigator adjudication. The bottom part is the clinical events committee. Now this is on the double endpoint, which is the primary endpoint for GUSTO IIb.

As you can see, the site felt there was a significant difference in the double endpoint at 30 days, where the clinical events committee didn't quite achieve that .05 value.

In the next slide, for Impact II, which was a trial of an anti-platelet inhibitor in patients undergoing PTCA, you can see for the composite endpoint, the CRF, which is the clinical report form of the investigator, found a significance difference in the triple endpoint in one arm versus placebo, where the clinical events committee did not find a significant difference.

The last slide assessing a discordance between the clinical events committee and the investigators is in the EPIC trial, which is another large trial of an anti-platelet agent, ReoPro, in patients undergoing PTCA.

You can see at the top part the table there for the primary endpoint. The investigators did not find a significant difference from either

treatment arm, but the CEC did find a very highly significant difference, at least in the ReoPro bolus plus infusion against placebo, not only for the primary endpoint, but this trend increasing the significance was also seen for the single endpoint of nonfatal MI and also for emergency room procedures.

So those are three recent trials that show similar sort of discordance and their effect on the investigator versus the CEC outcome.

CHAIRMAN MASSIE: Any other questions?

DR. GRINES: Well, I do think it's interesting that the doctor can't tell the difference between any of these drugs.

CHAIRMAN MASSIE: Okay. Why don't we take a break, try to get back in ten minutes.

(Whereupon, the foregoing matter went off the record at 3:28 p.m. and went back on the record at 3:45 p.m.)

CHAIRMAN MASSIE: Udho, you want to go ahead and ask questions?

DR. THADANI: Yes. A couple of questions. The FDA review said there was some difference seen between the heparin and the enoxaparin regarding to the left main disease, higher incidence in the heparin group, and the other one was high incidence of

ventricle arrhythmias. Has that been taken into account or could it have confounded the effects on --

DR. GENEVOIS: Eric Genevois from Biostatistics RPR.

We have identified three baseline characteristics which showed some slight imbalance between treatment groups at baseline. These were prior ventricular arrhythmia, three or more risk factors, and Q-wave MI at entry.

We have run Mantel-Haenszel tests on the endpoint at day 14 to evaluate the impact of this imbalance on the final outcome, and it turned out that the Breslow-Day test for homogeneity of the other issues were all nonsignificant, and that the Mantel-Haenszel p values of the treatment effects were all very close to the one that we obtained in the primary analysis, confirming that these imbalances have no impact on the treatment effect in the study.

Next slide, please.

The same analyses were performed on the three characteristics which were measured on study. The regimen of aspirin, which is the dose that was prescribed, was usually corrected after the treatment had been initiated. The information regarding the left main disease and the percentage of stenosis was

also measured after treatment had been initiated, and of course, the discontinuation of treatment within 48 hours with the reason of hospital discharge.

One more time, the Breslow-Day p values are nonsignificant, and the Mantel-Haenszel p values confirm the treatment effect except for the left main disease with more than 50 percent stenosis. It is to be noted, however, that this analysis only refers to less than half of the population, exactly 1582 patients with angiography.

DR. THADANI: A couple of other issues: One other issues comes up. As Professor Braunwald pointed out, heparin was recommended for intermediate and high risk patients, and yet in this trial all comers went in, because only about 40 or 50 percent of the patients had STT changes.

So a lot of low risk patients go in the trial. So is it really kosher to compare the aspirin data, which is Theroux's data with high risk groups, their STT changes and their analysis for all data, which includes low and high risk? Have you looked at the high risk separately from the low risk to see if there is a difference or should we not treat the low risk group with heparin or nothing at all? It's an important issue.

DR. COHEN: I'll remind you that the baseline characteristics revealed that close to 60 percent of the ESSENCE study group -- in fact, 57 and 58 percent -- 60 percent had ECG changes on admission which, if I'm not mistaken, was very, very similar to Theroux's original paper in 1988.

So in that regard, I think that these studies can be looked at in somewhat of a comparable light. In addition, the treatment effect favoring enoxaparin was very consistent along the majority of the pre-specified subsets, including some low risk subsets as well as high risk subsets.

There were only two pre-specified subsets that were low risk in which the treatment effect did not favor enoxaparin over heparin.

I'd like to add that in no subset was unfractionated heparin better than enoxaparin.

DR. THADANI: A lot of case has been made about a subgroup in 100-odd patients on the ambulatory monitoring. Yet only 40 percent of the patients showed some ST changes. I think it's hard to compare, because asked the question of rebound. Patients are lying in bed in the first 48 hours. You do the Holter monitoring, and the next forced drug treatment, they're ambulatory.

So I don't know even if it represents a bound, even if their incidence goes up, because they are more ambulating. You get more ischemia. They got triple -- you know, basal disease. So I think it would be premature. So the question is rebound should be asked in terms of clinical rebound; and when you're talking about Theroux's study, they were talking about clinical rebound.

So I think that has to be taken in context. Just a comment, because not necessarily means a rebound, because in both limbs it's going up. It's like doing the low level exercise in some of these patients.

One other concern always -- I think that was a final endpoint with the reinfarction. I can't remember if there's -- Was there a patient that had bypass surgery? It was not mandated by the protocol to have enzymes done routinely. So it's always a difficult situation. You have infarction on the patient. You have the enzymes, and unless they got Q-waves, you could have missed it, and even the echo is not required in every patient or NVT. So it's always -- you know, one wonders how many infarcts were really missed.

PTC, I think, is a requirement. Now

everybody is doing enzymes for first 24 hours, but I'm not aware of anybody doing in CABG, because nobody wants to report their infarct rate anymore. So have you got any comments or a feel, you know -- could you have missed some or something could have happened or is it a bias in any study design?

CHAIRMAN MASSIE: Are you looking for slides? It would be better if you could answer questions without slides. I mean, this is a question you probably don't really have a slide that can answer.

DR. FROMELL: Yes, you're right. We don't have, really.

This comment is an important comment, obviously, and I don't know any better answer than to say we just had such a small number of those kind of events to really comment easily on that.

I agree that, if we had required those in every single patient, that might have been a little more accurate, although again in a trial this size, that generally hasn't logistically been done. It's something to be considered, I guess, for future study.

DR. THADANI: And my last question is going to be: You arbitrarily divide infarcts, 16 hours as an arbitrary cut point. I've been on

committees. A major problem, even the pre-adjudication committee members can't agree sometimes.

Say, if a patient goes into trial at .2 hours post-admission, his first enzyme is normal, and there is no way of knowing that he was not already having an infarct or it is a silent infarct, despite the therapy. So wouldn't it be more meaningful not to separate out the infarcts, take all infarcts into account rather than worrying about reinfarction separating those, you know; because you are doing a post arbitrary division here.

How do you know a patient was not sleeping at night, and he infarcted, and his 16 hour value is up, and you're calling it was on admission rather than happened during therapy? It's always a concern to me, when you're adjudicating. I think there's a problem.

So treatments like this, you are trying to prevent an infarction, and you know, since you don't have all the data points before the entry, it becomes very tricky, at least in my assessment. So I want some comments from you.

DR. COHEN: Well, using the 16 hour guideline is not unique to this study. It was a guideline that, I think, I also saw in some of the other large clinical trials in an attempt to deal with

the issue of early reinfarction.

The fact of the matter is that, even an agent like troponin sometimes takes up to eight hours to become positive in a patient who at time zero is having a clinical event. So there has to be some way of discerning which patient is coming in with an index event and which patient developed an event because of failure of a trial therapy.

My perspective is that, as long as we're applying the same rules to both treatment groups, you know, we should be eliciting information that is reflective of whether or not there's a difference between the treatments.

So number one, the 16 hour rule is not unique to our study and, number two, it's applied fairly and in a blinded fashion to both treatment groups.

DR. THADANI: So what happens if you exclude -- Forget about 16 hours and just give total infarcts, irrespective of that, and see how many infarcts were in the two limbs, irrespective of hours.

DR. COHEN: The number of -- I could tell you that the absolute number of MIs occurring very, very early, within 16 hours, is a very small number. If you want, I think we do have that information

exactly, but I could just tell you from my recollection that it's a very small number.

CHAIRMAN MASSIE: John?

DR. DiMARCO: Dr. Grines earlier mentioned that she said that -- I think the quote was these must be pretty stable unstable angina patients, because one of the exclusions was you couldn't plan revascularization within 48 hours. Do you have an idea of how many patients were actually excluded for that reason? Is this really, truly a stable fraction of all patients with unstable angina?

DR. COHEN: We do not have the log of patients "screened" relative to, you know, actually enrolled. That would have been a relatively mammoth task for this size trial. With regard to their degree of severity or how dynamic a population they are, the only thing I can do is refer you to the baseline characteristics, 60 percent ECG changes, 60 percent prior aspirin users, 50 percent prior MIs, 20 percent prior PTCAs, 20 percent prior CABGs.

DR. DiMARCO: That's old data. That doesn't really tell us much about the acute situation except for the EKG changes. You know, I realize it's a problem, but I was just curious.

Did all of the centers have the ability to

do interventions or surgery in that center or were there some which would not have had that; so that might have biased what was happening?

DR. FROMELL: We had a wide variety of centers, as you can imagine. So there were centers that did not have a capability of doing revascularizations or invasive procedures.

DR. DiMARCO: Okay. So there may have been some subtle bias in terms of willingness of physicians to enroll then on that basis, because those centers -- their patients would have had to be transferred.

DR. FROMELL: We actually had a number of situations where we talked with the sites about having a predefined transfer hospital and a treatment period, if they felt comfortable, including the transport to the other facility. So we had scenarios where they had to stop drug and transfer, because the institution had no coordinator, or they would continue drug on transfer, because they also had a coordinator there.

Unfortunately, I don't know the exact numbers of those situations.

DR. DiMARCO: My last question was: A fair number of patients went on to have revascularization anyway. We heard a little bit about

extra bleeding around sheaths. Were there any other complications that could be seen in people who had either CABG or PTCA after the procedure, death, infarcts, other complications of the procedure?

DR. FROMELL: Actually, we don't have a comprehensive answer, but we do have one slide that shows the MI rates post revascularization, post CABG.

Could you cue carousel 3, slide 74?

So this is the MI rate post-revascularization in the heparin versus enoxaparin arm. You see overall, the rate is 30 in the heparin group for a 1.9 percent rate, and 22 in the enoxaparin group, for a 1.4 percent rate.

If you divide that to PTCA and CABG, you can see for PTCA it's equal, .5; and for post-CABG, it's 1.4 percent in the heparin group and .9 in the enoxaparin group.

DR. DiMARCO: Thank you.

CHAIRMAN MASSIE: Cindy, you said that you had one more question?

DR. GRINES: Oh, yes. I just wanted to comment on some of the other issues that were brought up, and one is, although I called this a low risk group, really it's not ultra low risk; because, in fact, every one of these patients that were enrolled

would have met criteria for receiving heparin, based on the unstable angina guidelines which say, if you have ECG changes or known coronary disease, you're supposed to receive heparin.

A second thing is that I think looking for Q-waves post-CABG is pretty standard, and it has not been routine in any institution to draw enzymes. So I don't have a problem with lack of enzymes in that population at all.

CHAIRMAN MASSIE: Okay, Mike?

DR. WEBER: I'm sorry to sort of backtrack to the beginning of the presentation, but one of the things that's pivotal in trying to get approval based on a single study is that there has to be a very credible hypothesis. I wonder if you could one more time talk about, without necessarily going back to a slide, remind me again of that part of the hypothesis that would have predicted the superiority of this newer compound compared with the nonfractionated heparin.

DR. RUSH: Well, we, obviously, don't know which of the possible reasons are the most important reason, and what I gave you was several that we think are likely to be contributors.

The first is that there is very little

patient-to-patient variability with enoxaparin, because you don't have binding to plasma proteins. So that the effect is very, very predictable, and that's an advantage over heparin when it's given intravenously.

Secondly, the level of anti-Xa activity -- and apparently -- I think we believe that that's a very important effect in arterial thromboses, and the absolute level of anti-Xa activity you obtain with enoxaparin is higher.

Then also this very important element of the platelet factor IX and the ability to inactivate heparin but not enoxaparin, I think, could play a very important role in arterial thromboses.

DR. WEBER: So these are sort of pharmacological or theoretical reasons, but was there any clinical evidence or even animal data that would make you believe that there would be a clinical advantage?

DR. PERRONE: I'm Mark Perrone. I'm in preclinical drug discovery in Collegefeld.

There are numerous data in the literature and in-house that have been generated and will soon be published that demonstrate that Lovenox inhibits smooth muscle proliferation. It has an anti-

inflammatory effect, and going back to the anti-Xa effect, by pacifying thrombin and keeping thrombin, you will prevent the thrombin mediated events and smooth muscle proliferation also.

DR. GRINES: Any clinical studies, though, like the DBT study showing it's superior to heparin? I think that's what maybe he was asking, clinical differences.

DR. WEBER: Because when you are using a hypothesis, the hypothesis in a sense has to have a power equivalent to having done a study, even though you haven't done precisely that study. I guess we need that reassurance.

DR. RUSH: Yes. The first DBT treatment study, the one that I mentioned in my talk, looked at thrombus size in the heparin treated group and the enoxaparin treated group. According to the Marter score, there was a significant decrease in the thrombin -- the size of the thrombus on venography. That's a pretreatment/post treatment test.

We've subsequently done two studies in DBT treatment. There's a trend toward superiority in the largest of these, but it was a 900 patient study. It was not large enough to demonstrate superiority of the 1 mg/kg twice daily dose over unfractionated heparin.

The conclusion of that trial, which has been filed with FDA, is that the two regimens are equivalent, but numerically there's a superiority of enoxaparin in the twice daily treatment group.

CHAIRMAN MASSIE: Marvin has a burning --

DR. KONSTAM: No, I just want to follow up on this line that Michael is opening, and let me just preface this by saying that this leading question that I'm about to ask doesn't influence approvability, in my mind, but it's a question for you.

Is there anything that convinces you that it is not correct that you could have achieved the same added benefit and added adverse effect with higher nonfractionated heparin doses, driving the PTT to a higher level? Is there anything inconsistent with that likelihood?

DR. COHEN: Well, I think that hypothesis was tested in TIMI 9A and in GUSTO IIA, that just simply driving up the APTT and getting more anticoagulation with standard unfractionated heparin was dangerous, and in fact both of those trials were terminated abruptly, and the dose reconfigured to a lower dose.

DR. KONSTAM: So what you're suggesting is that, with enoxaparin, there is somehow a shift in the

differential anticoagulant effect in favor of beneficial effects and away from adverse bleeding effects?

DR. COHEN: Correct, and the fulcrum for that may be anti-Xa activity relative to anti-IIa activity.

DR. KONSTAM: I'm not convinced.

CHAIRMAN MASSIE: Yes, Dr. Talarico?

DR. TALARICO: if we just consider heparin -- unfractionated heparin and low molecular weight heparin for their anti-thrombotic effect, irrespective of this being coronary thrombosis, there is now enough evidence -- there is innumerable evidence that low molecular weight heparin has proven to be as good as unfractionated heparin, if not better, for some indication. For example, for thrombi prophylaxis it seems to be better than --

So in that -- theoretically, there is enough experience to justify the assumption that this switch might have been worthwhile doing.

CHAIRMAN MASSIE: Let me just ask two questions. I mean, one is -- I'm thinking back to the guidance and, of course, the guidance is a smorgasbord of things to think about, and it's not a guideline for committees to act upon. I think that's important to

-- At least, that's the way I read it. That's why it's called guidance and not guideline.

In any case, the two things that I wanted to know is: If we're thinking about trials within trials, I guess the closest I can think of in this is that there's two different diseases. I accept that all of us think they're the same disease, really, non-Q-wave MI and unstable angina.

If you look at those two results separately using your triple endpoint, do you achieve statistical significance for each of them? I know that there's not a difference if you look at point estimates, but is there a significant effect for either or both of those endpoints independent of the combined?

DR. DURRLEMAN: No. Given the sample size we get, we do not reach statistical significance, although the same trends helps that.

CHAIRMAN MASSIE: I mean, that is my interpretation of when you have two clinical trials in the one, it's not that you have a heterogeneous population that is not different within itself, but rather you have combined a couple of things; for instance, a study in which you looked at stroke and heart attack and, you know, people going in and then

saw something different, and I know that is not one of the ones you emphasized as well, and you had a plus/minus, I think.

The other question was stimulated from the comment that you said you shifted partway through at the FDA's suggestion to formulating a hypothesis that heparin -- this was superior to heparin from an original equivalence. I guess one of the questions I would have is that this was designed as an equivalence trial from the beginning.

Knowing the way the FDA thinks about equivalence trials, why didn't you use a harder clinical endpoint as your primary endpoint? When you go to superior, I can see what you did, but if you go to equivalence, why didn't you design a trial to look at death in myocardial infarction?

DR. DURRLEMAN: Well, first of all, we considered that the treatment endpoint was a clinical and meaningful endpoint, and a robust endpoint. Now if we were to design a clinical trials based on, say, death and MI alone, then the sample size would be not this sample size, but much bigger.

CHAIRMAN MASSIE: So you jut didn't want to do a larger trial?

DR. DURRLEMAN: I think we were confident

also, given the data on enoxaparin, that we would be superior to heparin.

CHAIRMAN MASSIE: Okay. Well, as we get toward the end of this, a major discussion will be what is a clinically significant --

DR. MOYE: Barry, can I follow up on that?

CHAIRMAN MASSIE: Okay.

DR. MOYE: Thank you. Because I think one of the issues that this committee must address is the suitability of a single trial, a sole trial, for provability. I think at some point we have to focus our attention on the endpoint.

Now if I understood what I just heard, it is something that has become clinical trial lore in that, because of the small, sometimes vanishingly small, event rates, we cannot have trials that look at total mortality. I mean, that's kind of the sense, because it just costs too much. They're too large, logistically impossible and so on. However, we have to ask ourselves what price we pay for having a composite endpoint.

The important difference for me is that a composite endpoint in the analysis makes an assumption of analytic equivalence. That is to say, in the analysis, if I understood what I have read from your

work, a patient who has a recurrent MI counts the same as a patient who dies. Yet we know in clinical practice that's not the case.

We also know in this triple endpoint it's somewhat worse, isn't it, because we're assuming a patient who has angina analytically is the same as a patient who dies. So we have a little bit of a disassociation from the assumptions in the analysis disassociated from the clinical reality.

What happens is that it makes the endpoint difficult to interpret. Here we have an endpoint which is a triple endpoint, but from my point of view, really seems to be propelled not -- the efficacy seems to be propelled not by death and not by MI, but by unstable angina.

CHAIRMAN MASSIE: Well, I think that's some of the crux of what we need to talk about, and I think that's the crux of when you have guidance, and we have to fill in for this product, and others have to fill in for all other products what that guidance tells us. When it says clinically significant endpoint, what is the clinically significant endpoint, but we'll get to that.

DR. MOYE: I guess I just wonder -- For a sole -- to consider a single trial, can we have high

confidence in an endpoint that makes this kind of analytic equivalence which really doesn't stand up in the clinical arena? I mean, that's the question I'm trying to address.

CHAIRMAN MASSIE: I think we'll be discussing that, actually. JoAnn?

DR. LINDENFELD: Most of my questions have been answered. I just have one about the endpoint of recurrent angina. Can you tell me how many of those patients with recurrent angina actually had EKG changes, and how many of those were defined by rehospitalization or by revascularization; because I think the prognosis may or may not be somewhat different in those?

CHAIRMAN MASSIE: I'm not sure -- I interpret her question as saying, when they have the chest pain, are there ECG changes? I don't know if you have that information.

DR. LINDENFELD; I think that probably addresses it. I think, if that's triple endpoint, but it's angina with EKG changes, then that subset would probably be those.

As we talk about the endpoint, I wonder because, for instance, I think in the Delthauser reinfarction trial the patients who had recurrent

angina without EKG changes had the same prognosis as those who didn't have recurrent angina at all. So it would appear to be a lower group -- lower risk group.

CHAIRMAN MASSIE: In the meantime, did you have another question while they search for that one?

DR. LINDENFELD: No. That was my one that's left.

CHAIRMAN MASSIE: Are you ready?

DR. RUSH: I don't think we have a slide that breaks down the diagnosis based on EKG rehospitalization or revasc. We have the endpoint looked at all three of those ways.

CHAIRMAN MASSIE: Dan?

DR. RODEN: I have kind of philosophy questions, which we'll talk about among ourselves in a second, but there was one sort of thought that I had about the clinical use of this drug, and maybe this is sort of an imponderable.

It seems to me that one of the advantages of heparin is that, when a patient who's been in the hospital for 18 hours requires an emergency intervention, the heparin can be turned off and the intervention performed, and it seems to me the downside of this compound may be that that might be a more risky proposition.

So my question is how many patients required -- during the time they were receiving the new drug, how many patients required intervention compared to how many patients required intervention in the heparin arm, and what were the bleeding complications?

People are sort of nodding.

DR. THADANI: Dan, just one comment. For intervention for PTC, I just want to say we don't turn the heparin off. We actually continue it. So --

DR. RODEN: You turn it off for second and then turn it back on?

DR. GRINES: We never turn it off.

CHAIRMAN MASSIE: People have gotten so good, they don't have to.

DR. RODEN: I'm hearing a couple of hours down here. Every place is different. Well, just humor and do you have those data in terms of bleeding complications with interventions early -- I mean when patients were on therapy within two days?

DR. COHEN: What I can tell you is that we did is we altered the approach to removing the sheath. From a practical point of view, none of us are inhibited who do interventional cath in initiating the procedure and in doing the procedure when the patient

is anticoagulated, and our standard now is to continue aspirin, continue intravenous heparin, do the procedure.

The only impact of the antithrombotic therapy is on the timing of when you remove the sheath. What we provided to the investigators was a rough outline that, if the last dose of the subcutaneous trial drug was, you know, within four hours, we would ask them to wait an additional four hours to removing the sheath.

If it was beyond four hours, then they could wait a shorter time period before removing the sheath, because the peak activity of the low molecular weight heparin begins to dissipate after eight hours.

So it had -- We had an algorithm to follow with regard to sheath withdrawal. The actual number of sheath related complications: There was no difference in the major hemorrhages between the two groups with regard to bleeding around the sheaths, only a slight increase in the minor bleeds.

DR. LINDENFELD: But there were fewer interventions in the enoxaparin group. So that would be even slightly more than the slightly more. There were fewer total interventions -- am I correct? -- in the enoxaparin group; so the slightly more is slightly

more and slightly more.

CHAIRMAN MASSIE: Well, maybe we should move on to the philosophy and the voting.

DR. KONSTAM: Before we -- There's a point of clarification, I think, we could use. The question has been brought up about these missing patients, and Dr. Moye brought this up earlier. Could you clarify this again?

I guess the predefined endpoint is 14 days. So how many patients are missing from that primary endpoint, and what are we going to do about that -- at 14 days?

DR. RUSH: We -- The only way we have today to answer the question is that, of the patients that were missing by 30 days, we found two-thirds of them, and none of them had had an endpoint. So if we make the same assumption that two-thirds of the patients at 14 days were found, none of those had an endpoint, that means that -- what? -- there's a remaining -- There were 14 patients lost to follow-up at 14 days. Right?

DR. KONSTAM: Total, in both groups combined or just the enoxaparin group?

DR. MOYE: Fourteen total, six in the heparin group and eight in the Lovenox group.

DR. RUSH: Right. So 14 total. We found two-thirds of the patients lost to follow-up, and none of the patients we -- None of those patients had endpoints. So if we assume that we found the two-thirds of those 14, that means that only maximum of five are lost to follow-up at 14 days.

DR. DURRLEMAN: It would be two in the enoxaparin group, two in the heparin group, according to our best estimates of the data.

DR. KONSTAM: Okay. I just would like to state, I -- You know, we're going to have to go on on the basis of the information that we have, but I'd urge that this be clarified and that the FDA have a chance to review this and every attempt to be made to say what was the status of all patients at 14 days, and ask the FDA to clarify how much that changes things, and reflect back on our advice.

CHAIRMAN MASSIE: Okay. Well, again I don't think there's any point in reading this entire preamble before we get to the questions, but with regard to the guidance, I do want to read the section that we didn't see on the screen during the presentation.

It says -- It talks about reliance on a single study will generally be limited to situations

in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, such that confirmation of the result in the second trial would be ethically difficult or impossible.

Then it goes on to highlight some of the characteristics which we've seen presented to us about an excellent multi-center study with a powerful -- statistically powerful finding, multiple studies in a single study.

I think that's the important background. As I mentioned earlier, and I think we're all going to see in the future, these types of trials where equivalence is the only way to get at it are going to be coming more frequently, and I know Lem is not going to be happy, but composite endpoints are not going to go away either.

Perhaps we're going to be -- This is the one of the first times this committee has had to try to judge how powerful a composite endpoint really is or whether some components are more powerful than others, and perhaps our deliberations will be instructive to others some other time.

So let's start with the questions.

Was the ESSENCE trial an adequate and well controlled clinical trial that showed a significant clinical benefit of enoxaparin and -- added to aspirin, compared to heparin added to aspirin in the prevention of ischemic events associated with unstable angina and no-Q-wave MI?

To paraphrase that, the question is: Is this a positive trial?

DR. KONSTAM: Yes, I would say it is a positive trial, and I'd just like to stress the fact that, although we may have some concerns about the importance of the particular primary endpoint chosen, you know, I think we have to really give credit to the result of the trial in terms of it strongly meeting its predefined primary endpoint in a manner that, to my satisfaction, was established at the beginning of the trial.

I think that, okay, now we have to go back and say how important is that primary endpoint, but to me, I think this is a clearly positive trial.

CHAIRMAN MASSIE: Any other discussion and comments? Again, this is a trial not as an approval. This is judging the single trial on its merits.

DR. RODEN: Maybe I still want to know what the question means, because if the question is

does it demonstrate to our satisfaction, meaning using usual criteria for approvability, that it is better than heparin and aspirin, my answer would be no; because the -- no, not because it's not two trials, because the --

CHAIRMAN MASSIE: At least as I interpret this --

DR. RODEN: As it's written, is it -- you know, the answer is yes.

CHAIRMAN MASSIE: Okay.

DR. RODEN: But --

CHAIRMAN MASSIE: I think that's the way this was meant to be written.

DR. RODEN: -- this is the philosophy part.

CHAIRMAN MASSIE: No. This is not about approval. This is about --

DR. RODEN: Well, you know, you've changed one or two patients around, and you change a little endpoint around, and you lose all the significance. So in fact, that's why we would ordinarily ask for two trials, and that's why we're going to have this discussion.

CHAIRMAN MASSIE: All right. Well, we should probably vote on that.

DR. THADANI: Barry, just one comment. One of the difficulties also in the endpoints is the different thresholds of investigator for revascularization. I know my colleagues will send patients in post-attack of chest pain after they're on heparin. I sit on for hours, days. Being trained in Canada and England, so my threshold is much higher. So I think that's always a difficulty in angioplasty rate when I'm depending on the CCUs down to six, where it's at 36 in other months.

So one of the things you could also ask is what happens just for rehospitalization for unstable angina. I know you never showed that separate. It was always rehospitalization plus need for revascularization.

Rehospitalization, I think, is patient driven. The patient has to have severe chest pain. He has to go to ER. Someone sees him. Is there a difference if we just look at rehospitalization? I think that might be relevant, at least to the discussion.

CHAIRMAN MASSIE: Do you understand the question? It should be easy. You have death and infarction, and you have death and infarction and unstable angina requiring hospitalization. All you

have to do is subtract.

DR. THADANI: But it was never shown on any of the slides.

CHAIRMAN MASSIE: But there is no doubt, and I guess one of the strengths of a large, multi-center trial is they're going to capture physicians like you and physicians like Cindy, and presumably that's why single trials are being at least considered as representing larger groups' practice.

DR. THADANI: Yeah, I agree, because --

CHAIRMAN MASSIE: -- is whether different practice patterns could differentially affect the outcome of this trial.

DR. THADANI: That's the advantage of huge trials with a lot of different investigators, but I just want to know. It would be nice to know the trend is in the right direction, even for that.

DR. RODEN: While they're looking, Barry, can I ask whether the proposed indication -- whether the proposed labeling will say that the drug is superior to heparin or at least as good as heparin?

CHAIRMAN MASSIE: If it were to be approved? Maybe we should discuss that after.

DR. RODEN: Maybe that's what my concern is.

CHAIRMAN MASSIE: Well, Dr. Talarico, do you have any thoughts on that, if it were to be approved?

DR. TALARICO: No. That's what I'd like to determine.

CHAIRMAN MASSIE: You would like us to answer that question?

DR. TALARICO: Yes, that's right.

CHAIRMAN MASSIE: Okay, but we're not going to ask that question yet.

DR. TALARICO: If it is approved, how it should be labeled.

CHAIRMAN MASSIE: Okay. Any answer to --

DR. KONSTAM: Can I comment on that? I mean, we're jumping the gun maybe in terms of the discussion a little bit, but maybe it needs to be said that I think that there would be a substantial difficulty in approving this drug as equivalent to heparin when heparin -- unfractionated heparin, when heparin is not an approved drug for this use.

CHAIRMAN MASSIE: No, I think that -- Well, there are two possibilities, as I see it. One is you approve it for the condition, and the other is that you could say it's better than heparin and approved for the condition.

DR. RODEN: Right. Okay, but I don't --

CHAIRMAN MASSIE: You can't say it's equivalent to something that's not approved.

DR. RODEN: Right, but then -- Okay.

CHAIRMAN MASSIE: So the only -- If it's approved, it's got to be approved because it works in these patients.

DR. RODEN; I think the challenge for us is to define whether or not we can tell that it's different from placebo. That's really going to be the challenge. We can't approve it, I don't think, unless someone in the audience wants to correct us -- I don't think we can approve this drug because it's equivalent to heparin. I think we have to figure out from the data whether it's different from placebo or not.

DR. TALARICO: Heparin is not approved for unstable angina. Aspirin is, not heparin.

CHAIRMAN MASSIE: Right. Any answer to the number of patients rehospitalized for recurrent angina?

DR. RUSH: Overall, the number rehospitalized for recurrent angina was low, and it was equivalent in the two groups, 3.1 percent for heparin, 3.4 for enoxaparin for rehospitalization only, but that's cutting it into EKG changes,

revascularization decision prompting revascularization.

The other two categories accounted for a greater proportion of the patients counted for recurrent angina.

CHAIRMAN MASSIE: Okay. I'd like to --

DR. THADANI: Did you analyze that where there's no difference within treatment or the difference still holds?

DR. RUSH: You mean --

DR. THADANI: Is that MI and rehospitalization? I know it's not pre-specified.

DR. RUSH: Yeah, but that would be counting only a very small portion of the recurrent angina definition. I think that that would leave out a significant number of recurrent angina events that were important.

CHAIRMAN MASSIE: I don't -- Well, why don't we vote on the first question and get down to the more difficult questions, it sounds like. Do you want to start on whether this is an adequate and -- Oh, you can't vote?

DR. THADANI: I can't vote.

CHAIRMAN MASSIE: Okay. Whether this is an adequate and well controlled trial showing a

significant clinical benefit of enoxaparin.

DR. DiMARCO: I vote yes.

DR. GRINES: Yes.

DR. WEBER: Yes.

CHAIRMAN MASSIE: Yes.

DR. KONSTAM: Yes.

DR. LINDENFELD: Yes.

DR. RODEN: Yes.

DR. MOYE: Yes.

CHAIRMAN MASSIE: Okay. Are there specific characteristics of the ESSENCE trial that would make this single study one that provided persuasive and adequate support for the proposed indication? Possible characteristics include enoxaparin was superior to heparin, not only for the primary combined endpoint but for the separate recurrent MI and angina components of that endpoint.

DR. RODEN: You know, I'd like to address the issue in toto.

CHAIRMAN MASSIE: Actually, let me step back. I forgot to interject a question that I think we really need to consider before we do this, which is basically: There are a lot of components here, and there are a lot of combinations here, and I think it would be good for us as we continue this discussion to

get a sense for which of these we think are clinically important, irreversible morbidity or prevention of a disease with potentially serious outcome endpoints.

So I've made a list of six. The first is death, and I guess we probably don't need to vote on that.

DR. RODEN: What are you asking?

CHAIRMAN MASSIE: If this trial showed these things or if other trials showed these things, should they be considered -- other things being equal, adequate for approval based on a single trial? In other words, we decided we have a good trial.

If this good trial and something as good or better in the future showed these types of endpoints, would they be adequate to be approved based on a single trial, because this is what we're going to face in the future. Then we can use those types of standards to look at this trial.

I would say the first one is if mortality alone had been found in this trial, even though they started with a composite endpoint, would we consider that clinically important, meaningful, and sufficient for approval?

DR. KONSTAM: Well, I just want to clarify what's behind what you're asking, because you know, we

can -- I mean, I think this is a good exercise, but I wonder whether you're asking -- you're setting this up as the only possible criterion by which to accept a single trial.

CHAIRMAN MASSIE: No, no. There are all these other criteria, too, but in terms of a clinically important endpoint, which was one of the things that started off, and then some of the things you could look at, I think it's important. We probably won't agree on this, but at least we can discuss it.

I assume we all agree that a mortality trial --

DR. KONSTAM: You mean clinically important, irreversible endpoint?

CHAIRMAN MASSIE: Right.

DR. KONSTAM: That makes doing a second trial unethical?

CHAIRMAN MASSIE: Right, and would that actually be convincing in a single trial, even if it were not -- had not been the primary endpoint.

DR. KONSTAM: Well, I have a problem. There are two different issues. Okay? One is the degree to which you're convinced, and the other is the degree to which it would be unethical to do another

trial. I think there are two separate questions.

CHAIRMAN MASSIE: Well, let's focus on convinced now.

DR. KONSTAM: Okay, but you don't have to have an irreversible endpoint to be convinced.

CHAIRMAN MASSIE: That it's clinically important?

DR. KONSTAM: Yeah.

CHAIRMAN MASSIE: Okay, you may not have to. Some people may feel you do, but let's talk about it. Okay? But anyway, I don't think we need to talk about death. We've all said a mortality trial is good enough, and the agency has always acted on the proposition that a well done mortality trial would be sufficient as a single trial for approval.

DR. RODEN: Suppose in this trial there had been a slight reduction in mortality but an increase in recurrent angina and an increase in myocardial infarction. So that the composite endpoint came out a wash, because some of the endpoints went up and some went down, and the one that went down was mortality, but the ones that went up were the others.

DR. MOYE: I guess the best response I could give to that, that it's up to the individual. I mean, how much less of an endpoint is recurrent MI

than death? How much less is unstable angina than MI?

You know, I don't have the answer. I can't tell you seven-eighths, three-quarters, one-half. I don't think anybody -- I don't think anybody knows, but I think everybody believes that MI is not equivalent to death. That's kind of a conundrum we're in.

CHAIRMAN MASSIE: Well, Marv has some further comments on this.

DR. KONSTAM: Well, no. I just -- There are different ways to go here, Barry, and I think that one possibility is to really set up some rigorous exercises for the panel, and I would respect that, if you want to do that. Otherwise, maybe I could have an opportunity just to summarize sort of my feeling about the approvability and then go on to the other people.

CHAIRMAN MASSIE: At this point in time or when we get to that point, we'll discuss it?

DR. KONSTAM: Well, I would suggest this. If you'd like to set up an exercise, a rigorous exercise, such as the one that you suggested about asking which endpoints do we consider reversible and, therefore, approvable in and of themselves, let's go through that exercise and stick to it.

CHAIRMAN MASSIE: All right.

DR. KONSTAM: Otherwise, I have some -- If we want to just open it to general comments, let me begin with the general comments.

CHAIRMAN MASSIE: Well, we can do this either way. I think let's stick with this, and let's not get into the enoxaparin question yet. We've heard a couple of comments.

It's difficult, because if we get into these enoxaparin questions, we sort of lose track of what's clinically important, and I think that it's important to know what people feel is clinically important first.

DR. KONSTAM: Well, maybe I can comment on the general point. You know, I think that there are two different issues, and that's what I wanted to come back to.

I think that, to me, I think the approvability of a drug reflects the definitive, in your mind, identification that the drug does something beneficial to the patient. You're fairly sure about that, and that it's different from placebo.

I think, to me, that is an approval drug, and I think all of these guidelines then are set up sort of as a framework whereby we can reach that.

Now there is sort of a related but

separate question, which is: Is it ethical to do a second trial as a means of supporting the definitive nature of the finding? I think that's a related question, but it's not the same question. Okay?

So you know, I think those are a couple of the questions that we have to reflect on with regard to the dataset that we have. Are we convinced that the drug is different from placebo or are we convinced -- not totally convinced, but we're going to accept it as it is, because the endpoint is -- because it would be unethical to repeat the study, and we're not going to be able to rely on the usual standard of repeating it, because it's unethical to repeat it, because it's an irreversible endpoint.

There are important endpoints that are not irreversible.

CHAIRMAN MASSIE: I don't disagree, but you forgot -- There is a third dimension, which is: Are you totally confident that it would be reproduced if the trial were repeated, because that's why we have two standards. That's why the usual requirement is two trials, each --

DR. KONSTAM: No, that's my first point. My first point is: Is it different from placebo? The usual best standard for achieving that is two

reproducible trials, but I think every situation is different, and this one is a particularly challenging one, I think, and I think you have to bring everything into play to address that question with this dataset. Is the panel convinced that this drug is different from placebo, on the basis of whatever it has?

CHAIRMAN MASSIE: And we do have some guidance in terms of things, which is the next question when we get there; but one of them is that it be a clinically important endpoint. In fact, that's always one, even when you have two trials, that they should be clinically meaningful, as well as you're confident that they're correct.

DR. THADANI: Barry, just a comment, if I may.

CHAIRMAN MASSIE: No, I think we are going to get bogged down, and I see the light here; but I think that the important issue is what are these important enough to do, and then what characteristics of the trial might lead you beyond that?

I'd like to move on, and I think we all agree about death. Is myocardial infarction an endpoint that, in itself, meets the criteria of being clinically important and perhaps irreversible? Any thoughts on that?

DR. THADANI: I think myocardial infarction is absolutely important, because all we are doing is trying to prevent myocardial damage and final outcomes. I think it has to be important.

CHAIRMAN MASSIE: Does anybody disagree with myocardial infarction?

DR. THADANI: How you define infarction is a different issue, but the fact you admit the patient, you are trying to give medication to prevent an infarct. So, you know, how could you argue against it?

CHAIRMAN MASSIE: How about recurrent angina? I mean, if we had a trial that was performed and was highly significant and showed that it prevented recurrent angina in the hospitalization, would we feel that that as a single clinical trial with a high p value is enough to approve the drug?

DR. KONSTAM: Can I comment? Yes. Well, no, wait. Whoa. You asked a couple of different questions at the same time.

Do I think that that's an important endpoint that is the potential basis for approvability? Yes. I think, if you could show that a drug reduced the ischemic episodes convincingly, if you were convinced of that, yes. I think we have

drugs that are approved on that basis.

So my answer to the question, is it an important clinical endpoint, yes. Is it an irreversible endpoint? No.

CHAIRMAN MASSIE: How about other people?

DR. THADANI: I'm going to comment on that again for two reasons. I think here you have to differentiate between stable angina and unstable angina. Here you got a patient who has got prolonged chest pain. He has to be hospitalized. It's a very different issue than a patient whose activity varies on exertion, angina. He may get pain one day or another.

So if we concentrate on unstable angina, it's really for hospitalization. It's no different than revascularization for heart patients, which is one of the approvable criteria that you would use, need for hospitalization and death.

So I think, if you send a patient home and he is now to be admitted for recurrent or long chest pain at rest, I think it's an important endpoint. It may not be important, life and death, but at least the same for approval if you have a large enough trial and you go for that indication, I'm sure it should be approvable.

CHAIRMAN MASSIE: Any other thoughts on whether recurrent episode of angina in the hospital --

DR. TALARICO: Can I ask a question on recurrent angina? How come it's not important? This is what you need to do, go to revascularization or if that is what can be seen at MI?

CHAIRMAN MASSIE: I'm sorry?

DR. TALARICO: Recurrent --

CHAIRMAN MASSIE: Well, if it's going to proceed to revascularization, then one could look at the revascularization. If it's going to lead to an MI, but how confident we are -- I guess the reason we've asked this question separately is how confident are we that any given patient who gets an episode of angina is going to proceed to an MI or revascularization.

DR. TALARICO: Well, at least as confident as accepting the diagnosis they come in with. They came for unstable angina. They developed recurrent angina. Isn't this phases of treatment?

DR. GRINES: And Mike Ivins would say that patient should undergo catheterization and revascularization, if appropriate, but I consider that failure of medical therapy.

DR. TALARICO: Right.

CHAIRMAN MASSIE: Any other thoughts?

DR. LINDENFELD: I'm not sure recurrent angina alone, if that's the only positive thing, is enough to approve a drug on a single study. I think that's the question we're asking. If that were the only endpoint, is that enough? I think probably not, in the absence of any other data, on a single study.

DR. TALARICO: I was not referring to approval of a drug just on the basis of the fact of angina. I was just trying to understand the significance, the clinical significance of refractory angina as an event. I'm not saying that this by itself would be for accepting a single trial, but just the weight it carries.

DR. WEBER: But Cindy, could you clarify what you said? Someone who comes into a hospital with unstable angina and needs aggressive therapy for it, even if they don't have recurrent angina, what is their likely outcome? I mean, how important is it to prevent a recurrence of angina?

DR. GRINES: Oh, I can't really give you that data, but I do know that the guidelines state that, if you have recurrent angina on therapy, that's considered a failure of therapy, and you are supposed to proceed for revascularization, and this drug in

fact reduced the need for cath and revascularization.

DR. WEBER: But suppose the therapy succeeds? I mean, we're talking about a patient who's still got major coronary disease that's likely to finish up with the sorts of procedures you're talking about. So, to me, that's not anywhere near as important as a major irreversible pathologic event such as having a heart attack or, obviously, dying.

CHAIRMAN MASSIE: Well, I guess what we're reaching for is it is a surrogate for somebody who is more likely to infarct, as Dr. Talarico said, certainly more likely to get revascularized.

I guess the question I would have is do we need the surrogate or can we measure those outcomes? So another question is: Is angina that requires urgent revascularization different than a recurrent episode of angina, and does that become a more important clinical endpoint in people's minds?

DR. THADANI: But that's threshold dependent, isn't it?

DR. KONSTAM: Could I ask a question, just to help us clarify our thinking about this? Let's just say, for the sake of argument, that the sponsor were to repeat this study with exactly the same primary endpoint and have exactly the same results.

Would we then consider it approvable, because there are two different sets of issues, you know, just to clarify.

CHAIRMAN MASSIE: I think the answer is yes. I think there's been never a question about whether, if you add a placebo controlled study --

DR. KONSTAM: Okay. So --

CHAIRMAN MASSIE: We voted that we have one, but ultimately we're going to have to vote whether one is enough.

DR. KONSTAM: That -- I mean, this, I think, is a thing that Michael is groping with. Is this endpoint of angina at all important, you know. I mean, should it ever be in this setting the reason for approvability? I mean, I would answer yes. I think the panel is saying yes, but maybe there's not universal agreement on that.

CHAIRMAN MASSIE: I'm not sure.

DR. WEBER: The point I was also going to make is there's another issue here that you've already addressed, and we talked about very early, the assumption that we're not really comparing with placebo. We're comparing with another treatment, which is a treatment based on a guideline made by very experienced and knowledgeable people that we should be

using heparin and aspirin.

Now we've got something that we think is better than heparin and aspirin, but it's certainly not a placebo study. Suppose we discover that, in fact, despite all of our previous thoughts, heparin isn't all that it's cracked up to be. What are we left with?

CHAIRMAN MASSIE: I think that -- I guess we're going to have to go out of the conceptual into the real pretty soon, and that's the real; but I guess the last question I had, and I certainly have a feeling that there is a difference between angina that occurs and may not occur again and angina that leads the clinician to urgent revascularization, even though that may vary from clinician to clinician.

The presumption is, if you have a large number of clinicians, that would represent some different type of angina, and it certainly is an endpoint that has a certain morbidity and mortality itself attached to it, as well as the cost, as does rehospitalization, although I think the morbidity and mortality of the revascularization procedure is somewhat greater than that of a rehospitalization.

I guess that is where I personally would draw the line between clinically important, is not

just an episode of chest pain. Certainly, severe limiting chest pain, as Udho is pointing out, is something we approve drugs for, but we don't call it an endpoint in the same manner.

I don't know if anybody else would like to comment on that. Dan?

DR. THADANI: Do you want to mention something about the Vanquish trial that we --

CHAIRMAN MASSIE: No, I don't want to discuss the Vanquish trial.

DR. THADANI: No, I haven't said the results. You know, that's an important endpoint. Maybe rehospitalization might be more important than revascularization.

CHAIRMAN MASSIE: Well, I don't know if this exercise was worth doing or not, but let's move into the next set of question, which are -- We're dealing now with a specific trial in a specific circumstance, and the questions that come up, first of all, is: Is enoxaparin -- Was it superior to heparin not only for the combined primary endpoint but also for the separate recurrent angina and MI components?

Does that make it more convincing or convincing enough, I guess, is the question, to be adequate for approval as a single trial? Well, let's

read it again.

Are there specific characteristics of the ESSENCE trial that would make this single study one that provided persuasive and adequate support for the proposed indication? Possible characteristics that the agency has identified about this trial that might lead somebody, and perhaps us, to feel it is persuasive enough are -- and then the first one is the effect on separate endpoints, not the composite.

DR. KONSTAM: Could I exercise a little prerogative and just share some of my thoughts about where we are with this, because I think -- and then maybe come back to some of these specifics, because I think we're dancing around some issues, and maybe we need to get at them. So let me just share a couple of thoughts.

You know, I think, first of all, this whole set of questions is -- This whole issue is extremely challenging to me, and I'm not sure I know the right answer, and let's face precisely what the issue -- what the problem is that faces the sponsor and, therefore, faces us, which is that we have this situation where there is widespread use and clinical acceptance and, in fact, advocacy by the academic community of a drug that is not approved -- okay? --

and that's unfractionated heparin.

That's the backdrop with which we're going to have to work. It's the backdrop with which the sponsor has to work, and it's the backdrop with which we have to draw our conclusions.

So that, to me, is the enormous problem, and I'm not sure we have an answer, but I'll tell you how I go in trying to sort it out in my mind, and I'll just jump to tell you that I don't know really what the right thing to do is, but I'm leaning toward approvability in my own mind.

My thinking really goes something like this: The question is, do we have an effect that is important and potentially irreversible that's different from placebo? I think, you know, my guesstimate to the answer to the question is yes, and it comes from a combination of the fact that we have a single trial that met its endpoint, you know, to my mind, in a very clear way.

Then we start looking for endpoints that represent clear irreversible endpoints such as the combination of death and myocardial infarction. What do we really think this drug looks like compared to placebo with regard to the composite endpoint of death and myocardial infarction?

My best guess, based on all of the data put together, is clearly positive. I think that we have a strong, overwhelming stance on the part of the academic community that heparin prevents irreversible endpoints in the presence of this clinical setting.

We're dealing with a drug that is heparin and has some theoretical anticoagulant advantages, although we can't prove that, and then in that setting we have this drug beating heparin, beating unfractionated heparin in its primary endpoint, and the best analysis that we can come up with -- I don't know if somebody else -- Maybe Lem can come up with another analysis -- suggested to be highly probable, putting all the data together, that enoxaparin beats placebo.

So I come out with all of that saying in my mind, it is extremely likely on the basis of the dataset that we have that enoxaparin beats placebo on some very highly important and irreversible clinical endpoints.

Now am I right? Do I have a precise guideline to reach that? I don't know, and I think that's for the rest of the panel to decide.

CHAIRMAN MASSIE: I think we've heard that, and that really is 2(d), I think, on the list of

possibilities.

DR. KONSTAM: I just thought I'd summarize my --

CHAIRMAN MASSIE: But I think it's important as we talk here today that, realize, this trial we're comparing enoxaparin to heparin. We're going to have this whole same set of questions next week or last meeting, for that matter, where we had a single trial comparing a drug to no heparin.

DR. RODEN: We want to know what took you so long, Ray.

CHAIRMAN MASSIE: And the same questions come up.

DR. KONSTAM: I've been waiting for this moment.

CHAIRMAN MASSIE: Anyway, before Ray speaks, I really don't think that we should jump to the idea that, just because heparin is here in the first intellectual sense of how we evaluate these data, the same process is going to have to go on someday where there's no active comparator; but, obviously, we -- I think we all recognize it as an active comparator, and that's why there's a specific question related to that as perhaps being the thing that convinces you, as it does Marvin. Ray?

DR. LIPICKY: Whether or not you know that heparin works in combination with aspirin, you haven't seen any data at all in that regard. It may be very convincing. Whether it's approved or not is irrelevant, if the data would show that it is convincing.

You haven't seen that. So you don't know anything about it, but that doesn't mean that you don't have enough information to make a decision, and you have what makes something look like it's better than heparin.

So the decision making that you have to do, it seems to me, is the usual paradigm that people follow is two trials with a p of .05. That's sort of the equivalent of a single trial with a p of .0025. Okay? That makes it powerful and believable as a single trial. This p doesn't approach that, even for the combined endpoint.

Then secondly, if the combined endpoint doesn't include irreversible harm and you are not convinced that irreversible harm, cell death, is attributable to the drug, prevention of cell death, then there is no reason to feel compelled to make a decision on the basis of a single trial, and one could ask for the paradigm to be satisfied with two trials

with a p of .05 or two trials with a p of .019.

So I think that that's the nature of the problem.

CHAIRMAN MASSIE: Yeah.

DR. LIPICKY: It's how convinced you are. You know, you can declare a trial positive. That's okay, but it's not convincing enough.

DR. KONSTAM: Ray, part of the problem I have -- part of the problem I have with this is that we haven't looked at the heparin data in sufficient detail, and I think that's a real problem; because I'm concerned -- I follow that logic completely, but the concern that I have is, if we go in now and do another trial, it's entirely possible in my mind that you wind up with the same triple endpoint that now moves into not quite statistically significant range versus heparin.

In my mind as a clinician scientist, I think that is posing a substantial problem to the sponsor and to us in trying to determine what really is important here, which is whether the drug differs from placebo.

DR. LIPICKY: Well, convincingly; and that's the aspect of convincingly, and what you would consider to be convincing. I hate to reduce that to

p values. It's just easier to put it in those terms with respect to whether or not you have a drug effect, but it's really how convincing it is or how persuasive it is.

CHAIRMAN MASSIE: And, in fact, I think what you're seeing everybody struggling here with is how to put this data in the context of our imputed effect of heparin and come with a combined p value that might be or might not be less than .0025.

DR. LIPICKY: I recognize that problem.

CHAIRMAN MASSIE: And you don't think it's a valid one perhaps, but that's what everybody here is saying.

DR. LIPICKY: No, I understand that.

DR. RODEN: Ray, does it influence -- or should it influence our thinking that this is not exactly a new drug, that it's been around for a long time, that it's been evaluated under conditions in which sort of clotting does case morbidity and mortality and has been shown to be superior to placebo? So we have sort of a basis --

DR. LIPICKY: You mean what should your basing in prior be?

DR. RODEN: Right. I mean, we have a base, and we also have some basic science and some

clinical correlates of that basic science to think that this actually makes sense.

DR. LIPICKY; Well, that's philosophy, too, and I can only give you my opinion, and that is it shouldn't influence your thinking.

CHAIRMAN MASSIE: Okay. Well, let's try to get back to the questions with that reorientation perhaps.

We're here with (a). Heparin will come up later, and it clearly has to come up, because I think it's not the same, as Marvin has elegantly pointed out, but the fact that there are multiple components at least or multiple ways of looking at this primary endpoint in this trial -- does that influence us to feel that it is persuasive enough as a single trial to warrant approval?

Maybe the answer is we should vote and not talk. How about that? Lem?

DR. MOYE: Okay. I would vote --

CHAIRMAN MASSIE: We're answering 2(a), which we've read three times.

DR. MOYE: Okay. I would vote the statement 2(a) does not bolster my support for this trial as a single study.

CHAIRMAN MASSIE: Okay. Dan?

DR. RODEN: Whatever Lem just voted, I think I disagree with him. Was that a yes or was that a no?

DR. MOYE: I don't think 2(a), the statement that heparin was superior -- enoxaparin was superior to heparin not only, and so on -- I don't think that strengthens the argument for a single study.

CHAIRMAN MASSIE: Well, I think what it's saying is that we have a primary combined endpoint. That was significant. We all decided that was significant. The fact is that it also beat the endpoint of various definitions of recurrent angina. It did not beat the endpoint, actually, of either myocardial infarction or the combination of death and myocardial infarction, I think, if I remember the data correctly.

So I'm not sure exactly what's in this question, in fact, but we've been asked it. We should answer it.

DR. WEBER: Lem, if this had been two separate trials and one had had a myocardial infarction endpoint and the other had had an angina endpoint, but you now have two studies, albeit with related but different endpoints, would that be

satisfactory to you?

DR. MOYE: I have -- If you're saying to me that I have two independent studies, independent sets of patients, independent sets of investigators, they had prospectively defined endpoints, one had a primary endpoint of fatal and nonfatal MI, the other had a primary endpoint of what?

DR. WEBER: Recurrent -- What have we got here? Recurrent angina.

DR. MOYE: I think -- I mean, in the hypothetical sense of the question, I would answer yes.

CHAIRMAN MASSIE: Dan, do you have a feeling enough to vote?

DR. RODEN: My answer is no.

CHAIRMAN MASSIE: JoAnn?

DR. LINDENFELD: No, for just this one, but there will be several that I think add up over time.

CHAIRMAN MASSIE: Right. We get a chance to do that.

DR. KONSTAM: I'm not sure this question deserves a vote. I mean, I guess -- I'm not sure what we're voting on. I think that, if I have a composite endpoint, I think the fact that each of the components

of the composite endpoint are going in the same direction gives me some solace that it's not being driven solely by some unimportant component of the composite endpoint.

DR. MOYE: Marv, that's fine, but that's not true here. That's not true here. I mean, death didn't --

DR. KONSTAM: No, I'm not -- I guess this, to me -- That's why I don't think it's worth voting on. I think this is --

CHAIRMAN MASSIE: Oh, okay. You can vote or abstain. That's possible.

DR. KONSTAM: Okay, I'll abstain.

CHAIRMAN MASSIE: Okay. I'll vote no.

DR. WEBER: I'm going to abstain for the same reasons as my friend here. I just don't understand the question.

DR. GRINES: No.

DR. DiMARCO: No.

CHAIRMAN MASSIE: Okay. Now (b), 2(b) -- that the unspecified but often used endpoint of death, MI and recurrent angina prompting revascularization at 14 days was very strongly significant in its own right, I think. At this point, we're not talking about the heparin as a comparator, but just that this

was positive. I think we should phrase that question, because the heparin really comes in in 2(d).

So now we have a positive endpoint, non-pre-specified, but found of an endpoint that is often used in clinical trials, some components of which people were impressed with. Let's start at the other end. John?

DR. DiMARCO: Well, as I understand the question, it is whether this endpoint, which I believe is positive and I think it's an important one, is enough to make this single study adequate support for the proposed indication. In that case, I'd say no.

DR. GRINES; Is that the question?

CHAIRMAN MASSIE: I think, as I read it -- Is that the question?

DR. TALARICO: Yes.

CHAIRMAN MASSIE: That's the question.

DR. GRINES: Oh, okay. I think it's very significant. I think these are statistically significant and clinically significant, and I would vote yes for this one.

DR. TALARICO: This, of course, is a competency test using recurrent angina and revascularization instead of recurrent angina alone.

DR. GRINES: Right.

DR. WEBER: No, I would vote yes on this for this combined endpoint.

CHAIRMAN MASSIE: Well, I'm going to vote no, not because I don't think it's significant, but partly because it wasn't designed that way, and partly because I think its significance is much enhanced when we think of the fact that heparin was the comparator and not placebo; because I'm not sure as a single trial. If it was against placebo and it had the marginal statistical significance, the .0025 standard, then I would vote yes. So I'm going to vote no here.

DR. GRINES: Well, could I ask a question about this? I mean, I thought that, since we have active controls, that we shouldn't expect as much benefit as compared to placebo; because I think most of us clinicians, at least that deal with coronary disease, strongly believe that heparin is an important therapeutic --

CHAIRMAN MASSIE: Maybe -- I'm just trying to interpret the question as I see them. I think that that's where point (d) is supposed to come in, where it says that it was compared to a probably active agent. So I guess we're trying to look at the endpoint separate from the comparator in some way, although in the end we have to look at them together,

obviously.

So I'm just interpreting the questions as right now asking if we had a trial that was designed at this composite endpoint, happened to find it was positive but also found at post hoc analysis that the revascularization was positive at the level we found it, that -- you know, that we would then say this is enough as a single trial to approve the drug. I guess we've had some votes. Marv?

DR. KONSTAM: Yeah. I'm going to vote yes, that the fact that this unspecified endpoint was strongly positive just pushes me in the direction of a willingness to accept the dataset as it is toward approvability.

DR. LINDENFELD: I would say no, although this pushes me, I think, as a single thing. It doesn't push quite enough to say yes.

DR. KONSTAM: Is the question whether this is a single thing? I think -- What are we voting on?

CHAIRMAN MASSIE: The fact that -- We've decided that we have a positive trial.

DR. KONSTAM: Which possible characteristics include. I mean, I'm interpreting that we're trying to pull everything together and make a judgment, not that we have to meet one single --

CHAIRMAN MASSIE: Maybe we're talking the same language, that we should wait to pull everything together until we ask when we put everything together how we vote. Okay? I think what they're saying -- and maybe I could translate it in a different way.

Somebody designs a trial to look at Drug X against placebo, makes this their endpoint, gets a p value of .019 as a single trial. Are we going to approve it?

Now, obviously, there are a lot of nuances within the trial, and how each of the composite endpoints all do and all the rest. So we can't say anything in general, but if it looked nice, would we approve it for that endpoint or would we say do a second trial?

DR. KONSTAM: You know, I think what we're looking at are factors that in aggregate will tend to -- could tend to lead us to the conclusion that we don't need a second trial. I don't think we're looking for a single thing to say, yes, if it meets this one, then it's a go.

I think -- You know, I think, yes, this is something that pushes you in that direction.

CHAIRMAN MASSIE: Well, I agree, but as JoAnn says, it doesn't push me far enough,

particularly in the setting where we have no difference in death, and death and infarction.

DR. KONSTAM: It wouldn't push me far enough, in and of itself, either. I mean, if that's what we're voting on, then the answer is no.

CHAIRMAN MASSIE: I think that's what we're voting on.

DR. KONSTAM: I'm saying, yes, it pushes me in that direction.

CHAIRMAN MASSIE: No. Would you approve it as a single trial?

DR. KONSTAM: There is not going to be one thing that pushes me all the way to approvability. It's looking at all of these points in aggregate.

CHAIRMAN MASSIE: Okay. So he votes yes. JoAnn?

DR. LINDENFELD; It pushes me, but not enough on this single item to say yes. So I'll say no.

CHAIRMAN MASSIE: Okay.

DR. RODEN: No.

DR. MOYE: I continue to have continued extreme difficulty in unspecified endpoints in any trial, single, companion, any shape or form.

CHAIRMAN MASSIE: Okay. So that's a no,

because it wasn't something that was specified in advance, which was actually an important consideration for me as well.

Okay. That the advantage was still present at 30 days. Is that enough?

DR. MOYE: No.

DR. RODEN: No. As I understand all these post hoc analyses, I mean, it all makes somebody feel warm and fuzzy, but I always have this suspicion that, if they didn't turn out quite as positive, we wouldn't hear about the post hoc analyses. For that reason, I vote no.

CHAIRMAN MASSIE: Okay.

DR. LINDENFELD: No.

DR. KONSTAM: Yeah. I would vote no to this. This, to me, is not a point that pushes you toward approvability. To me, this is more a defensive issue. It would be very disturbing if it were no longer true at 30 days, and it's reassuring that the primary endpoint is correct, that it's still true to 30 days.

CHAIRMAN MASSIE: I would agree, and I would vote no.

DR. TALARICO: It has a pre-specified --

CHAIRMAN MASSIE: Pre-specified secondary

endpoint.

DR. TALARICO: -- secondary endpoint. Right.

CHAIRMAN MASSIE: In that way, it differs from the revascularization, which was a post hoc.

DR. KONSTAM: Well, I would still stick to what I was saying. I don't see this particular point, that it's still true at 30 days, as pushing me toward approvability per se.

CHAIRMAN MASSIE: I'd like to emphasize that, you know, one point in time --

DR. KONSTAM: It would be bad if it weren't true.

CHAIRMAN MASSIE: It would be bad if it wasn't true, because I think we did review something a month ago where they made the 30 day endpoint there, and it was there at some number of days or hours, and then it wasn't there at 30 days, at least in one of the groups, and we were impressed negatively in that sense. So --

DR. WEBER: Yeah. I think it is important that it was still present at 30 days, but I guess, in and of itself as a single finding, it wouldn't persuade me. So I guess I'm a no-er, too.

DR. GRINES: No.

DR. DiMARCO: No.

CHAIRMAN MASSIE: Okay. Now we get to the more problematic issue, the issue of the fact that this was not a placebo controlled trial. It was against an active comparator, and we don't need to reiterate the preamble or all the previous discussions we've had.

The comparator is not an approved drug. The data are not as rigorous as modern trials would now require to get it approved. It's a meta analysis of some open label, some placebo controlled trials, but it's there, and that's why the company had to do this trial in this manner.

I guess this question is to ask us how that, together with the other evidence we have, would impact on our decision. Ray is reminding us that we should be certain that, if there had been -- if there were a placebo controlled trial now, that it would be highly likely at a p less than .0025, if we had the wisdom of Solomon to know what placebo would do in the setting.

I guess that's the level of confidence we have to have, and maybe -- Do we need any further discussion or have we discussed this ad nauseam? I

think the second part of this is what is it? What's specific about what you think the impact of this is on the inference?

I guess one way we can interpret it, that is with endpoint that we found in this trial, do we think that -- Well, let's vote yes or no on this, and then we can discuss which endpoint we're talking about. So I guess we'll start at John, at your end, and the fact that the results we've seen have to be in a trial that was controlled with heparin may influence your decision.

DR. DiMARCO: I think this is probably the masterful argument, if you're going to argue for approval. I'd feel a lot stronger in voting for approval, though, if we had changed -- seen change in what I see as the really irreversible endpoints, like MI or myocardial infarction, because those are -- If we had seen changes there, that's what I think would prevent doing another study.

So I'm going to say, yes, I do think it should influence our thought, but I still don't think this is an adequate single criterion.

CHAIRMAN MASSIE: So I guess, the way we're counting the votes now, that's a no.

DR. DiMARCO: That's a no.

DR. GRINES: Well, I'm strongly influenced by the fact that it was compared to an active agent. We really have no other alternative. The only drug that's approved is aspirin. None of the new anti-platelet agents are approved for this indication. There's no anti-thrombin agent approved.

I don't know anybody in this country that would treat an unstable angina patient with just aspirin alone, and the fact that Lovenox is superior to heparin, I think, is of clinical importance. So I don't know which way I vote. Is that a yes or a no?

CHAIRMAN MASSIE: That's a yes, I think.

DR. WEBER: Yeah, I feel the same way. I mean, we have to assume at this point that it is the standard of care to use heparin along with aspirin. We're not going to do a placebo trial. I think Cindy has made that pretty clear.

So if we have a standard of practice which is to use heparin along with aspirin, and now we've got something that seems to be better than it, then I think we have to be persuaded.

CHAIRMAN MASSIE: That's a yes, I think.

I'll vote yes as well, and I think that it's a shame that we divorced the first and second phrases there, because I'm voting yes not because this

trial was positive against heparin, but because I think that there are endpoints that I think are clinically important and irreversible that I'm imputing are positive against heparin.

So it's not the first vote where we used the composite endpoint. It's the analyses of death and infarction or, for my comfort, death and infarction and revascularization, which would be more different, that I think are positive -- would be positive against an imputed placebo at a level that would be lower than .0025 and perhaps lower than .0001.

I'm not sure where it would be, but I'm quite confident from these results that, had we had a placebo arm here, it would be highly significantly different for a clinically important endpoint.

DR. KONSTAM: Yeah, I'm going to vote yes, and I have to -- I guess I agree with just what Barry said, that this point with regard to the relative benefit of unfractionated heparin is likely to be the thing that is driving me toward a leniency toward approving the drug on the basis of the current dataset.

I have to say, though, that, you know, what Ray said is really troubling me, which is that we

haven't reviewed the unfractionated heparin dataset, you know, in this form, and we would have been on a little bit firmer grounds if we had looked at that critically as opposed to the only thing we did here is rely on the sponsor's analysis.

I think, to me, that's the critical issue. I think that, if we could come to the conclusion on the basis of the heparin dataset and the present study that it is overwhelmingly likely that the drug differs from placebo in important endpoints, then I think we would approve the drug, and I think we haven't fully analyzed the dataset.

CHAIRMAN MASSIE: JoAnn?

DR. LINDENFELD: I'm going to answer yes to this. I think I might not be willing to quite answer yes, but in light -- I know we're answering just one at a time, but I think there's enough things now that I believe heparin is probably an active agent. It's at worse neutral, but almost certainly has some small effect. So I think this would tip me over.

I know we're supposed to be on one, but still I'd say yes.

CHAIRMAN MASSIE: Dan?

DR. RODEN: I'll say yes.

CHAIRMAN MASSIE: Lem?

DR. MOYE: If there is no evidence that heparin beats placebo, then for me there's very little solace in enoxaparin beating heparin. So I vote no.

CHAIRMAN MASSIE: Okay. Well, we did have a chance to review some of those data, and I guess we didn't have the package there. We didn't review it here.

DR. KONSTAM: We haven't heard the FDA.

CHAIRMAN MASSIE: But I guess the last thing I'd feel obligated to get out of this question, though, is the second phrase here. What -- If, for instance, the composite endpoint was what we thought we could beat heparin on, but there was not much of a difference between the active comparator for death and infarction, would we still feel the same way or is it because we think that the difference has been not just for a composite endpoint that includes something that at least we've debated as to whether it's clinically significant enough is there; because I guess this issue will come back to us, too, and we need to know that.

What's your feeling on that?

DR. KONSTAM: Well, you know, I think, to me, there's two things. One is we have one strong --

in my view, strongly positive trial, and then my willingness to accept that is this imputed effect versus placebo on the irreversible endpoint of death or MI.

So I'm in my mind imputing what I believe that effect to be, and I'm using that to support the fact that we have one clearly positive trial, and that's how I'm viewing it.

CHAIRMAN MASSIE: Any other comments? Is that what you wanted to hear from us?

DR. TALARICO: Yes.

CHAIRMAN MASSIE: Okay. We have a couple more questions, and then I think Dr. Talarico has suggested one more that we need to discuss that isn't here.

What about the information from other trials or do you want us to go that far? Yes. So the positive FRISC and the negative FRIC? Does that help?

DR. KONSTAM: I mean, it helps me, not -- It helps me interpret the dataset, because it supports, you know, the general construct of why this drug would work. It's other evidence that other preparations of unfractionated -- of low molecular weight heparin are beneficial, and so it doesn't

directly impact on the dataset except to create a general informational framework that says, you know what, I really believe the findings that we have.

CHAIRMAN MASSIE: Any other comments on that? We've traditionally not used, you know, data from one drug to another, but I think psychologically when we get down to the stuff with the ACE inhibitor which nobody ever asked us about anyway, probably for the same reason, that those types of things do affect us; but of course, here the other drugs aren't even approved for this indication, but it's still something out there.

You want us to vote on that, whether or not another--

DR. TALARICO: If you want to.

CHAIRMAN MASSIE: I don't think we probably need to. I'm sure that we might have thought differently if that other low molecular weight heparin didn't beat placebo.

DR. KONSTAM: I mean, it gets at -- I mean, you really have to deal with the question of how different you think this agent -- these two agents are. I mean, if -- You know, if you believe that the effect seen in the FRISC trial is a heparin effect, and you believe that the -- you know, that the

anticoagulant effect of enoxaparin and dalteparin are similar, then you really start saying, you know what, I mean, this thing works. Low molecular weight heparin works.

So I think that the amount of weight that you place on it really depends on how much you believe you're really dealing with, you know, a common drug.

CHAIRMAN MASSIE: I guess the answer is it's sort of like the 30 day endpoint. If it hadn't been consistent, we would have had second thoughts. If we had a negative trial against placebo with a similar drug, I'm not sure we would have jumped to one drug being adequate evidence.

DR. GRINES: Well, it either strengthens -- They're not the same drugs, but it either strengthens the fact that low molecular weight heparins work as a general group or that heparin itself -- something about heparin itself is effective. Either way, it supports the current --

CHAIRMAN MASSIE: So I guess the final -- second to final question, because we've been asked to comment about what we're approving it for in terms of relationship to heparin -- so we'll save that -- that the question is: In light of your answers to question 2, do you believe that the ESSENCE trial provides

substantial evidence of the effectiveness of enoxaparin for the proposed indication?

I guess we better reiterate what was the proposed indication. I guess it's for -- the primary endpoint for prevention of death, myocardial infarction and recurrent angina in the presence of patients presenting with unstable angina and non-Q-wave MI?

DR. TALARICO: I assume that would be the composite.

CHAIRMAN MASSIE: Or something to be wordsmithed by the agency perhaps.

DR. GRINES: I have a bit of a problem with these composite endpoints in that they always include death, when in fact none of these agents -- none of the antithrombin or anti-platelet agents have affected mortality at all.

It's not that I'm opposed to, you know, these combined endpoints, but it really bothers me when it's plastered on the headlines of USA Today and these companies advertise that it reduces death, when it fact it doesn't.

I wonder whether the FDA would consider taking the portions of the primary endpoint that really are important and approving it for that

indication rather than death.

DR. RUSH: Did you want us to restate the indication?

CHAIRMAN MASSIE: Well, why don't you state your words for the indication?

DR. RUSH: Okay. Treatment of unstable angina and non-Q-wave myocardial infarction concurrently administered with aspirin.

DR. LINDENFELD: You know, I have sort of the same kind of problem that Cindy commented on, but I think we're saying that MI is a surrogate for death, and that's why we're accepting a smaller study. So in other words, including it in the composite isn't necessarily inconsistent, if we're saying that these other endpoints indicate that we can get an endpoint with fewer patients.

CHAIRMAN MASSIE: Well, I think Cindy has got an important point, because you know, if you include everything in your composite endpoint, that allows you to advertise it, even though it wasn't positive that that is a real issue. I think we have to face up to the fact that this trial does not show that this drug reduces death.

DR. KONSTAM: You know, this came up in the carbetalol stuff, too, because it was the same set

of issues of composite endpoint and how the wording came, and at least that point Dr. Temple said he can deal with it.

I know the wording wound up including the word death in it, and I think I have some concern about that. I mean, I agree with the spirit of the concern, but you know, I think this could be dealt with in the labeling.

CHAIRMAN MASSIE: Well, I think the answer was that the indication did not include death. I think it was -- but in the clinical pharmacology --

DR. KONSTAM: Well, morbidity and mortality, including -- you know, and supports a study that showed a result that included the reduction.

CHAIRMAN MASSIE: But I personally think the endpoint -- I mean the indication you talked about is probably correct. It's for treating people with this disease, and I think that's -- So maybe we should -- Dr. Talarico, did you --

DR. TALARICO: The issue here were if the drug were to be approved, what indication should it be approved for; because if you notice in our question, the first paragraph includes the treatment of unstable angina in quotes; and to tell the truth, I don't understand really what that refers to, what would be

the treatment of unstable angina.

It has to be specified better what exactly a treatment would accomplish, and it could be the combined endpoint of death and MI. The recurrent angina could be part of it.

CHAIRMAN MASSIE: Okay.

DR. GRINES: I guess I don't have a problem with talking about the combined endpoints, but I think that there should be a qualifying statement that mortality was not reduced.

DR. TALARICO: The labelling would particularly include the results of the critical time. So, therefore, there would be information of what the efficacy had been found to be in each of the three parts of the indication.

CHAIRMAN MASSIE: So there's an indication. The indication usually says for the treatment of this to accomplish that, but the question is do we have to say what we're accomplishing or just say it's indicated for the treatment of it?

DR. TALARICO: Right, but I'm not sure I understand what would be the treatment of unstable angina.

CHAIRMAN MASSIE: The treatment what? I couldn't hear you.

DR. TALARICO: The proposed labelling says for the treatment of unstable angina, and I think this is not very satisfactory.

CHAIRMAN MASSIE: What would you --

DR. TALARICO: What is the treatment of unstable angina? What exactly does the treatment accomplish?

CHAIRMAN MASSIE: Ah, okay.

DR. TALARICO: It's very vague and unclear. If you say this is indicated for the treatment of unstable angina, I don't think that would suffice.

CHAIRMAN MASSIE: Well, I think that this is going to be difficult for a committee to decide, but I think what we are talking about is we're treating non-Q-wave MI, of course, and unstable angina, and the goal is to prevent recurrent ischemic events and the complications of these conditions.

DR. TALARICO: Yes, but that should not be implicit. It should be specified.

CHAIRMAN MASSIE: So what we're trying to prevent is either infarction or recurrent ischemic events.

DR. TALARICO: Right.

CHAIRMAN MASSIE: The complication is

some of these people will die. This trial didn't show that we prevented those deaths.

DR. TALARICO: Should we specify whether it's approved for the indication is for prevention of death, MI and recurrent angina or the prevention of recurrent angina and MI or whatever it is?

CHAIRMAN MASSIE: Well, I'll just propose that it's for prevention of myocardial infarction and recurrent ischemic events and their complications. How about something like that? In the end, you're going to have work it out a little bit better than we're going to come up with here on the committee.

I think the sense we're saying is that we don't want to say in the indication this is to prevent death, because we haven't seen a prevention of death in this data, although we may all assume that, if you prevent enough MIs, you will prevent some deaths.

We have to vote whether we want to approve it for anything.

DR. TALARICO: Okay.

CHAIRMAN MASSIE: So, Lem?

DR. MOYE: I vote no approval, because both the construction of the primary endpoint and the efficacy findings are each too weak.

CHAIRMAN MASSIE: Dan?

DR. RODEN: The -- I would vote yes, if I felt that it would be "unethical" -- that's a very emotionally charged word -- to deny this treatment, because it were demonstrably superior to something.

I think I am convinced, because as compared to what I believe is an active control, that the drug is effective for what it's claimed to be effective -- I don't think a second trial is necessary. I'm not sure I will use the word ethical. So I will vote yes.

CHAIRMAN MASSIE: Well, you're saying you don't think it's unethical to do another trial, but you don't think you need to?

DR. RODEN: I don't think you need it, no, and I think -- I don't think I like the term, you know, it's ethical to or it's ethical not to, and maybe I shouldn't have introduced that; but I think that there's enough data here to convince me.

DR. LINDENFELD: Yes, I also would vote for approval. I think that this is not a strong a study as we would like for a single study, but it is a strong study, and then it's supported by a number of other things, the previous data, the theoretical reasons, the Holter data.

I think there's a whole lot of little

things that make me say that this drug should be approved.

DR. KONSTAM: I'm going to vote yes, but I'm going to quality it. My rationale for voting yes is the combination of one clearly positive trial and the imputed effect on the combined endpoint of death and mortality compared to placebo; but -- and -- but I'd like to reiterate that I don't feel that we as a committee have fully reviewed the unfractionated heparin dataset.

Furthermore, I would like the FDA to do its own analysis on what the imputed effect on that endpoint, death or mortality, is. We've heard the sponsor's analysis. I haven't heard an FDA analysis, and I'd like the FDA to do that analysis.

I'd just like to point out, you know, the problem that we have of the entire cardiology community having gotten ahead of the regulatory process in this particular situation with regard to heparin, and I think that's why we're in this bind that we're in, and I would urge that we do something to correct that.

So it's a qualified yes.

CHAIRMAN MASSIE: Well, I'm voting yes, because, simply put, it's incredibly hard to beat a

drug that I believe works for a clinically important endpoint, and I think I've seen that happen, and God knows how I could defend how well I think that drug works, but I think the evidence are pretty strong there, and that's why I would have also voted yes for the guideline that said we should use it.

DR. WEBER: Yes, I think I'm going to agree with Barry. I must admit, I started out somewhat skeptical, because I wasn't sure of the strength of the data to support the use of heparin, but having listened to the presentation this afternoon and the opinions of my learned colleagues in this area, I have to accept that heparin, to the best that it ever could be, under the circumstances, is a proven treatment, and that we've now seen a study that, I think, was a well executed study and showed that this new product is able to beat heparin.

I really can't see any alternative other than to approve its use.

DR. GRINES: I vote yes.

DR. DiMARCO: Although I agree with everyone that this is a positive study, I still don't feel it's strong enough to meet the guidelines for approving a single study. So I'll vote no.

CHAIRMAN MASSIE: Okay. I don't know what

that vote was. Six to two. Did we lose -- Oh, that's right. We have two excluded.

I guess the one comment: You can see from the way we've struggled with this that, if you're going to go against an imputed placebo, you better really beat the drug, not just for an endpoint that you pre-specified but for one that's also clinically important in the future and beat it very handily, if not handily enough for everybody on the committee.

I don't know. Dr. Talarico did ask us to make some comment about the relationship, whether it's better than heparin. Do you --

DR. TALARICO: We have not completed yet our own analysis of the comparison of the meta analysis, I think, but I would have liked to discuss a bit more the endpoint approved -- not endpoints, the indications for approval, whether this should be death, myocardial infarction and recurrent angina.

DR. RODEN: Can I ask what the indication for the thrombolytics is? What is the stated indication for the thrombolytics, for example? Does it state for the treatment of myocardial infarction or does it state for the treatment of myocardial infarction to prevent X, Y or Z?

DR. TALARICO: The approval for aspirin,

for example, is approval -- prevention of death and --

DR. RODEN: How about for the thrombolytics?

DR. TALARICO: Thrombolytics -- I don't know. Ray has left.

CHAIRMAN MASSIE: Well, I think what you've heard is that we don't think there's evidence to prevent death, and I think that there's clearly evidence to prevent recurrent ischemic events in this population, and one of those recurrent ischemic events is myocardial infarction.

I guess some wordsmithing around using those words is what you need to do, but I don't think we can as a committee sit here and work out the best wording for this.

DR. TALARICO: Right.

CHAIRMAN MASSIE: Except for the sentiment that it should not say it's to prolong survival or to prevent death.

Any other thoughts or comments on that? That seems to be what everybody is looking for.

Well, I think that we've covered this ground. I don't know if there are any further questions. It's a difficult problem, one that's going to be coming to us more and more frequently, I'm

afraid.

Thanks, everybody, for their time.

(Whereupon, the foregoing matter went off the record at 5:34 p.m.)

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