UNITED STATES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

87TH MEETING

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Friday,

January 29, 1999

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The Meeting took place in the Natcher Building, Main Auditorium of the National Institute of Health, 45 Center Drive, Bethesda, Maryland at 9:00 a.m., Chairman Milton Packer, presiding.

MEMBERS PRESENT:

DR. MILTON PACKER, CHAIRMAN
JOAN C. STANDAERT, Executive Secretary
DR. CINDY M. GRINES
DR. JOANN LINDENFELD
DR. LEMUEL MOYE
DR. MARVIN KONSTAM
DR. DAN RODEN

CONSUMER REPRESENTATIVES:

D R . T H O M A S G R A B O Y S

DR. ILEANA PIÑA

GUESTS:

DR. JAY COHN
DR. RAYMOND LIPICKY

ALSO PRESENT:

MICHAEL CROCKETT
DR. ROBIN ALLGREN
DR. DARLENE HORTON
DR. WILLIAM ABRAHAM

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S (8:35 a.m.)

CHAIRMAN PACKER: This is the 87th meeting of the Cardiovascular and Renal Drugs Advisory Committee.

The NDA under discussion this morning is Natrecor, the generic name is Nesiritide. The sponsor is Scios Nova, the indication is for the short-term treatment of congestive heart failure.

Joan, will you read the conflicts of interest for this morning?

SECRETARY 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 for the meeting, and all financial interests reported by the Committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 USC 208 B3, full waivers have been granted to Dr. Robert Califf, and Dr. Udho Thadani. A copy of these waiver statements may be obtained from the Agency's Freedom of Information office, room 12A30, of the Parklawn Building.

We would also like to note, for the record, that Dr. Califf, through his employer, the Duke Clinical Research Institute, has interest in Pfizer, Eli Lilly, manufacturers of a competing product, Natrecor.

Although these involvements do not constitute a financial interest in the particular matter within the meaning of 18 USC, they could create the appearance of impartiality.

However, the Agency has determined, notwithstanding these interest, that the interest in the Government in Dr. Califf's participation outweighs concern that the integrity of the Agency's programs may be questioned.

Therefore Dr. Califf may participate in all matters concerning Natrecor. However, he will not

be here today.

In addition we would like to disclose that several of our participants reported previous involvements with Natrecor that really should be disclosed.

FDA believes that it is important to acknowledge a participant's involvement, so that their participation can be objectively evaluated.

Dr. Piña's employer, the Temple University, previously participated in the short term trial of Natrecor. Although Dr. Piña was named as a sub-investigator on the study, she had nothing, whatsoever, to do with the trial.

Dr. Packer would also like to note that he was involved in the early development of Natrecor, as a consultant, but his participation in the program ended more than two years ago.

Dr. Packer's employer, the Columbia University College of Physicians and Surgeons, was involved in a phase II study of Natrecor. Dr. Packer was listed as an investigator on the study, but did not participate in the recruitment of patients, or the

analysis of the data.

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.

And that concludes the conflict of interest statement for today.

CHAIRMAN PACKER: We normally reserve time for public comment. Is there any public comment?

(No response.)

CHAIRMAN PACKER: Then we will move forward, and ask SCIOS Nova to proceed with their presentation on today's NDA.

MR. CROCKETT: Chairman Packer, members of the Advisory Committee, good morning. My name is Michael Crockett, and I'm the Associate Director of SCIOS Inc., not SCIOS Nova, but SCIOS Inc.

Today SCIOS will present to you the development program for Natrecor, a new therapy for congestive heart failure. SCIOS filed a new drug

application for this product in April of 1998.

The agenda for today will include my brief introduction, followed by a presentation from Dr. Robin Allgren, from SCIOS, on the efficacy profile of Natrecor.

Dr. Darlene Horton, also from SCIOS, will present Natrecor's safety profile, followed by concluding remarks from Dr. William Abraham, who will discuss the benefit risk assessment. Dr. Abraham is from the University of Cincinnati College of Medicine.

My introductory remarks will first include the indication statement, as submitted to the FDA, and also included in your copy of the briefing document. I will then provide a brief discussion of the nomenclature, followed by an outline of Natrecor's regulatory history.

I will conclude with a description of the key agreements between SCIOS and the FDA, which shaped the clinical development of Natrecor.

The proposed indication statement, Natrecor, Nesiritide, is indicated for the short term intravenous therapy of congestive heart failure, or

CHF.

In patients with CHF Natrecor rapidly reduces pulmonary capillary wedge pressure and systemic vascular resistance and increases cardiac index. It also causes rapid symptomatic improvement.

The scientific name for Natrecor is human B-type naturietic peptide, or hBNP. In the literature HBNP is sometimes referred to as brain naturietic peptide. The proposed USAN name, currently under consideration, is Nesiritide.

SCIOS utilizes a recombinant manufacturing process to produce the 32 amino acid peptide product with the trade name Natrecor.

SCIOS has demonstrated that Natrecor is chemically and structurally identical to endogenous HBNP.

The IND for Natrecor was filed in November of 1993. Clinical development commenced in January of 1994, and an end of phase II meeting was held in July of 1996, and the clinical pre-NDA meeting took place in July of 1997, and finally as I stated earlier, SCIOS filed the Natrecor NDA in April of 1998.

Over the course of development, from 1993 to 1997, through a series of meetings, SCIOS and the Agency reached agreement on a number of key issues that helped shape the development program for Natrecor.

The key agreements reached between SCIOS and the FDA include the following: First, for approval, improvement in pulmonary capillary wedge pressure over a short period, versus placebo, is an appropriate primary efficacy endpoint.

Second: Other hemodynamic parameters and clinical status should be monitored. And, thirdly, a safety data base for the NDA should include approximately 500 patients treated with Natrecor.

As stated earlier, SCIOS began the development of Natrecor in November of 1993.

Natrecor's clinical development in heart failure has been consistent with the proposed guidelines from December 1987, which described the evaluation of drugs for the treatment of CHF, in particular, the guidelines specifically state: For a short-term drug, usually an intravenously administered

agent, the data base with respect to safety usually consists of several hundred patients, ie, 200 to 400 treated for varying periods.

A large number should have received the drug for periods of 24 to 48 hours, and some for periods up to 5 to 7 days.

Informed by these understandings and agreements for our program, SCIOS is eager to present to the Advisory Committee this promising new treatment for congestive heart failure.

I would now like to introduce Dr. Robin Allgren, from Scios, who will discuss the efficacy profile for Natrecor.

CHAIRMAN PACKER: I think it would appropriate to simply include in the record that the guidelines that you referred to in 1987 were, in fact, re-reviewed a year ago, at a meeting of this Committee, particularly as it relates to the utilization of IV drugs, and also new guidelines for the treatment of heart failure were reviewed by this Committee within the last 12 months.

It is also relevant, in that regard, to

simply note for the record that the last time this Committee actually had the opportunity to review an IV drug for the treatment of heart failure was, in fact, in December of 1987. That was IV Milrinone.

This Committee has not seen an IV drug for the treatment of heart failure in 11 years. So it is not clear how all of these guidances should, in fact, be incorporated. So I think most importantly we need to look at the data, and see what the data, in fact, would indicate to us.

MR. CROCKETT: Duly noted, and without further ado, Dr. Robin Allgren.

DR. ALLGREN: Thank you, Mike. Good morning.

I would like to now review the clinical data which demonstrates that Natrecor Nesiritide is an efficacious agent for the short-term treatment of CHF. These data show that when Natrecor is administered to patients with decompensated CHF, it results in beneficial effects on both cardiac hemodynamics and clinical status.

These are the topics I will be discussing

this morning. First, I will briefly review the pharmacology of BNP, then I will review the Natrecor clinical development particular with emphasis on four key studies; study 307, an early dose ranging study, the two pivotal efficacy studies, studies 311 and 325, and finally study 326, the last and largest study in the development program.

I will conclude by discussing our recommendations for dosing. We are recommending that Natrecor be administered at a fixed dose infusion at a dose of 0.015 microgram per kilogram per minute, without a loading bolus. And I will discuss the rationale for that recommendation.

As you know, heart failure is a major health problem in the United States, affecting over five million americans, and leading to over one million hospital admissions each year.

When patients present with decompensated CHF their cardiac dysfunction is characterized by elevations in cardiac pre-load and after load. And they present with symptoms of congestion, such as dyspnea.

When these patients are hospitalized the goal of therapy is to rapidly stabilize their cardiac hemodynamics and reduce their symptoms, with the goal of returning them to a more compensated state, which can be maintained on oral medications as out patients.

Human B-type naturietic peptide, or HBNP, is a 32 amino acid peptide synthesized by the ventricular myocardium. Plasm BNP levels are elevated in patients with heart failure with both systolic and dystolic dysfunction.

And BNP is believed to be one of the bodies own natural compensatory mechanisms in response to cardiac dysfunction.

The main pharmacological properties of BNP are summarized here. First and foremost BNP acts as a balanced vasodilator. In vitro, and in vivo, in animals and humans, BNP has been shown to have vasodilatory effects on both venus and arterial tissue, including coronary arteries.

In vivo this leads to a reduction in pre-load and after load, with a resulting indirect increase in cardiac index. BNP has no direct

inotropic activity. BNP's vasodilatory effects are mediated by the binding of BNP to cell surface receptors, the stimulation of guanalate cyclase, and the production of cyclic GNP as a second messenger.

BNP also has neurohormonal properties which counteract the vasoconstrictive neurohormonal activation, seen in CHF. For example, in multiple studies, BNP has been shown to decrease plasma aldosterone.

In addition, in multiple studies, BNP has been shown to increase diuresis and natriuresis. This is believed to be a direct effect of BNP on the kidney, primarily at the level of the distal renal tubule, but also may be mediated indirectly via BNP's effects on aldosterone.

Thus, you can see, overall BNP has a pharmacological profile which would be beneficial to patients with CHF. Therefore Scios developed Natrecor Nesiritide as an IV agent for the short treatment of CHF.

Natrecor Nesiritide has the identical amino acid sequence to the endogenous HBNP peptide.

BNP, or Natrecor has been studied in eight controlled clinical studies in patients with CHF. Throughout the development program a reduction in pulmonary capillary wedge pressure has been the primary efficacy endpoint, as agreed to, with the Agency.

The effects of Natrecor on wedge pressure have been studied in seven randomized double blind placebo controlled studies, and the results of these studies are shown here at a very abstract schematic level.

In each study the effects of placebo on wedge are shown in blue, and the effects of Natrecor at the various doses studied in each study are shown in yellow.

I show this slide to simply make the point that in every study in which wedge pressure has been measured, Natrecor has resulted in a reduction in wedge pressure.

I will now proceed to discuss some of these individual studies in more detail, beginning with study 307.

Study 307 was a randomized double blind

place controlled study enrolling 20 patients with symptomatic CHF. Each patient received an escalating dose infusion of Natrecor and placebo, on consecutive days, in a crossover design.

The doses of Natrecor administered are shown here on the X axis, and they were 0.003, 0.01, 0.03, and .1 microgram per kilogram per minute. So you can see this study covered a wide range of doses.

At the lowest dose administered minimal to no effect on various hemodynamic parameters was observed. As the dose of Natrecor was increased, dose related and plasma concentration related effects on hemodynamics were seen.

These included reductions in pre-load, as measured by reductions in pulmonary capillary wedge pressure, and mean right atrial pressure. Reductions in afterload, as characterized by reductions in systemic vascular resistance, and dose related increases in cardiac index were seen.

These were accompanied by modest dose related reductions in blood pressure, no effect on heart rate was seen at all but the highest dose.

Now, as you can see, the highest dose studied in this study resulted in very potent hemodynamic effects. Its use, however, was limited by the frequent development of symptomatic hypotension. This dose was, therefore, dropped from subsequent clinical evaluation. But the lower doses were well tolerated.

Thus this study showed that Natrecor administration results in dose related hemodynamic effects, and that doses in the range of .01 to .03 micrograms per kilogram per minute, are the likely optimal dose range for patients with CHF.

And these doses were studied extensively in subsequent clinical studies.

I will now move on to discuss the pivotal efficacy studies, but first I would like to review the demographics of patients enrolled in these studies. The mean age of patients was age 61, and 42 percent were age 65 or greater. Over a quarter of the patients were women, and over half of patients had CHF due to ischemic cardiomyopathy.

The vast majority of patients had NYHA

class III and class IV CHF. Thus, you can see, these patients had the demographics typical of patients presenting for hospitalization with decompensated CHF.

I will now review the design of the two pivotal efficacy studies, studies 311 and 325. Both studies were randomized double blind placebo controlled studies.

Study 311 enrolled 103 patients with symptomatic CHF. Study 325 enrolled 127 patients with symptomatic CHF. But it is important to note that these were patients with severe decompensated CHF, severe enough to require hospitalization and IV vasoactive therapy.

Thus these patients are representative of the patients who will be treated with Natrecor upon commercialization.

Both protocols required that at enrollment patients have a pulmonary capillary wedge pressure of at least 18, and a cardiac index less than or equal to 2.7.

Study 311 furthermore required that the patients have an ejection fraction less than or equal

to 35 percent, whereas study 325 had no such restriction on ejection fraction.

The doses administered in the two studies are shown here. Both studies were parallel designed placebo controlled studies, in which study drug was administered as a fixed dose infusion preceded by a small loading bolus.

The doses of Natrecor administered in study 311 are 015, 03 and 06 micrograms per kilogram per minute. And in study 325, the 015 and 03 doses were administered.

Now, in study 311, study drug was administered for a fixed 24 hour dosing period. Now, in study 325, you remember, these are patients who are quite ill with acutely decompensated CHF. And, therefore, in that study, patients randomized to placebo were only required to stay on placebo for the first six hours, then they were allowed to transition over to an active control agent for the short term treatment of CHF, such as Dobutamine or Milrinone.

For patients randomized to the Natrecor group in study 325, the duration of Natrecor

administration was left to the discretion of the investigator. It turned out to be a mean of 36 hours, with some patients receiving drug for up to five days.

In both studies the primary efficacy endpoint was reduction in pulmonary capillary wedge pressure, at three and six hours, respectively.

Now, the results of Natrecor on the primary efficacy endpoint for both studies are shown here. These graphs show the effect of study drug on wedge pressure over the first six hours of infusion in the two studies, with study 311 on the left, and 325 on the right.

You can see that Natrecor rapidly resulted in statistically significant reductions wedge pressure compared to placebo, even at the first high point assessed in each study.

Now, if one analyzes the effect of Natrecor on wedge pressure at six hours, using an intent to treat carry forward analysis, one achieves highly statistically significant results with a P less than 0.001 in both studies.

Now, it should be noted that both of the

protocols actually specified a primary analysis methodology that was different from an intent to treat carry forward.

In study 311, this was a per protocol analysis of those patients who remained on the drug of randomization through three hours, and in study 325 this was a worst outcome nonparametric analysis.

I'm not planning to review the results of those analyses in detail here, they were provided to you in the briefing document. I will just briefly mention that both of those analyses yielded results which were very similar to the results obtained in each study for the intent to treat carry forward analysis.

And the results were also highly statistically significant in both studies, with a P equal to 0.004, and less than 0.001 in the two studies, respectively.

Thus, highly statistically significant results were obtained for the primary efficacy endpoint for both pivotal efficacy studies 311 and 325 when analyzed either by an intent to treat carry

forward methodology, or by the protocol specified analysis methodology.

Now, in these studies we also looked at the effect of Natrecor on other hemodynamic parameters. And this shows the results of that for study 325. Again, remember, this study enrolled patients with acutely decompensated CHF requiring hospitalization.

And we could again see, even in these acutely ill patients, that Natrecor has the hemodynamic profile shown here, characterized, again, by reductions in pre-load and afterload, increases in cardiac index, modest dose reductions, modest reductions in systolic blood pressure, with no effect on heart rate.

In addition, in study 311, we've had the opportunity to look at the effects of Natrecor when administered in a placebo controlled setting over 24 hours. The effects of Natrecor on wedge is shown at the top, and on cardio index is shown on the bottom.

You can see that Natrecor had sustained effects on hemodynamic parameters through the 24 hour

infusion. It is also worth noting that at the time the study drug infusion was stopped, hemodynamic parameters rapidly returned to baseline levels, as would be expected.

Thus study 311 demonstrated that Natrecor has sustained hemodynamic effects through 24 hours of infusion.

So to summarize the effects of Natrecor on hemodynamics, Natrecor has been studied in seven randomized double blind placebo controlled studies, and at each of these studies Natrecor has resulted in a reduction in pulmonary capillary wedge pressure.

Of note, highly statistically significant results were obtained for the effects of Natrecor on wedge pressure at the primary efficacy endpoint in the two pivotal efficacy studies, studies 311 and 325.

Study 311 also shows that Natrecor has sustained hemodynamic effects through 24 hours of infusion. Multiple studies show that Natrecor has a desirable hemodynamic profile characterized by reductions in pre-load and afterload, and an increase in cardiac output.

And this hemodynamic profile is obtained without an accompanying increase in heart rate.

Now, in addition to looking at hemodynamics, in study 325, we also looked at the effects of Natrecor on clinical status. You will, again, remember that study 325 is a study which enrolled patients with acutely decompensated CHF, requiring hospitalization. And it began with a six hour randomized double blind placebo controlled assessment period.

At the end of that six hours, the patients were asked how they were feeling, or were asked to rate their own clinical status according to a five category scale, as either markedly worse, worse, no change, better, or markedly better.

And the percent of patients reporting feeling better, or markedly better, in other words reporting feeling improved, is shown here on the left.

As you can see, very few placebo patients reported an improvement in their clinical status by six hours. On the other hand, over 60 percent of Natrecor patients reported an improvement in clinical

status.

This improvement was highly statistically significant, when compared to placebo, at a P less than or equal to 0.001 for each of the Natrecor dose groups.

In addition, at the end of the initial six hour period, the physicians were also asked to asses each patient's clinical status, and to similarly rate it on a five category scale.

And you can see that similar results were obtained, as shown here on the right. Again, very few placebo patients were reported as being better, whereas over 60 percent of Natrecor patients were showing, or rated, as having an improvement of their clinical status.

Thus, Natrecor has been shown to improve clinical status when compared to placebo, when assessed either by the subjects themselves, or by their physicians.

Now, in addition to looking at global clinical status, we also looked at individual symptoms of CHF. These were dyspnea, fatigue, light-

headedness, and decreased appetite.

At the end of the six hour period the physician and subject, together, were asked to rate the subject's symptoms as either worse, no change, or better. And the results are shown here.

Again you can see that very few placebo patients are reporting an improvement in any of these system. However, a significant number of Natrecor patients are reporting an improvement in each of these symptoms, and a number of these comparisons are significant when compared to placebo at a nominal P less than 0.05 level.

Thus, Natrecor has been shown to improve both global clinical status, and specific symptoms of CHF, when compared to placebo.

Now, the next question we asked was, was there any correlation between the effects of Natrecor on hemodynamics and on clinical status, or specific symptoms such as dyspnea.

One of these analyses are shown here. What was done here is for each subject their dyspnea rating at six hours was plotted on the X axis in one

of the three rating categories.

And, for each subject, the percent change in wedge pressure at six hours was plotted on the Y Axis. And a couple of interesting observations can be made.

First, regardless of treatment group, one can see, that in general, patients who report an improvement in dyspnea also tend to have reductions in pulmonary capillary wedge pressure.

In addition, if one now looks at patient's by treatment group with placebo patients shown in blue, and Natrecor patients shown in yellow and green, one can see that in general it is the Natrecor patients who are experiencing both an improvement in dyspnea, and a reduction in wedge pressure.

Placebo patients, on the other hand, tend to either have no change, or a worsening of dyspnea accompanied by an elevation in wedge pressure.

While this certainly does not prove a causal relationship between hemodynamics and clinical status it does suggest that they are correlated.

Now, up until now I've been talking about

the initial six hour period in study 325. But we did continue to follow up patients after that time period, and I would now like to briefly review that information.

On the far left here you can see the results which I've already shown you, for the subjects self assessment of their clinical status at six hours, and as I showed you, very few placebo patients were reporting feeling better, while about 60 percent of Natrecor patients were reporting feeling better.

Now, patients were followed over time, and they were again asked how they were feeling at 24 hours and the end of therapy. By 24 hours you can see that about 80 percent of patients assigned to the Natrecor groups are reporting an improvement in clinical status.

Now, after six hours the placebo patients were crossed over to an IV vasoactive agent for the treatment of CHF, such as dobutamine or Milrinone. And after 18 to 24 hours of therapy on those agents, you can see they are also now reporting an improvement on clinical status.

We continued to follow patients through the end of therapy, which ranged from 22 hours to five days. And you can see by that time period, approximately 90 percent of Natrecor patients are reporting an improvement in clinical status, a response rate comparable to that being seen with the standard care agents.

Thus this suggests that patients assigned to the Natrecor groups experienced a continuous improvement in clinical status through 24 hours and the end of therapy.

I will now move on to review study 326, the final study in the clinical development program. This study enrolled 305 patients with decompensated congestive heart failure.

And it is, again, important to note that these are patients with acutely decompensated CHF requiring hospitalization and IV vasoactive therapy.

Now, this was not an efficacy study, per se. The goal of this study was to collect additional safety and clinical experience information with Natrecor when administered in a setting most like

actual clinical practice.

For that reason this protocol was very non-restrictive with regard to inclusion/exclusion criteria or protocol methodology.

Treatment decisions, such as the duration of dosing, or the use of concomitant medications were left to the discretion of the investigator. The protocol also did not require central hemodynamic monitoring, and therefore it was left to the discretion of the investigator whether or not to use a Swan-Ganz catheter.

A Swan-Ganz catheter was used in less than 20 percent of patients enrolled in this study.

Now, when patients were enrolled they were randomized to one of three treatment arms. They either received the 015, or the 03 dose of Natrecor, or were assigned to the standard care group.

Now, patients in the standard care group received IV vasoactive agent of the investigator's choosing, such as dobutamine, Milrinone, or nitroglycerin.

Treatment assignment was open label as to

whether patients were receiving Natrecor or standard care. However, the two Natrecor dose groups were double blinded. This was so that knowledge of dose assignment would not bias investigator's treatment decisions, or the reporting of safety events.

Now, I reiterate, again, that this was not designed as an efficacy study, per se, and therefore the protocol did not pre-specify any criteria for demonstrating either the equivalence or superiority of Natrecor to standard care.

The purpose of the standard care arm was to allow us to collect information on the natural history of patients with CHF as they are currently treated. This study was designed primarily to collect additional safety and clinical experience, information in a clinically relevant setting.

Now, the safety information from this study will be discussed extensively by Dr. Horton in her safety review. But I do mention this study as part of the efficacy review, because some efficacy parameters were measured in it, such as measures of clinical status and symptoms, and I would like to

review those with you.

First I want to review the study drug dosing. 203 patients received Natrecor in one of the two dose groups. And the standard care agents received by the control patients are shown here.

You can see 57 percent of patients received Dobutamine, about 20 percent each received Milrinone and nitroglycerin, and a few patients got Dopamine.

The duration of dosing is shown here in the bottom module, and you can see, for Natrecor patients, it was between 44 to 51 hours of a mean duration of infusion, but some patients got infusions for up to 7 to 9 days.

It is also important to note in this study that this study was intended to look at Natrecor as an initial IV vasoactive agent for the short treatment of CHF. In other words, patients were excluded who had already received other IV vasoactive agents for more than four hours.

In addition, in this study, it is important to note that patients who were kept on their

initial study drug assignment, throughout the dosing period for this study, it was very rare for additional vasoactive agents to be added.

Thus this is really looking at Natrecor as the sole vasoactive agent for the treatment of these patients.

Now, as I mentioned in this study the subjects were also asked to asses their own global clinical status. In other words, they were asked how they were feeling at six hours, 24 hours, and the end of therapy.

The results at six hours are shown here. And, again, you can see, in the yellow and green bars, that after six hours of therapy about 60 percent of Natrecor patients are reporting feeling better.

This response rate is very similar to what was seen in study 325, even though that study was being done in parallel by a different set of investigators.

It is also important to remember, in this study, the control patients are not receiving placebo, they are receiving an IV vasoactive control agent,

such as Dobutamine or Milrinone. And you can see that about 60 percent of these subjects are also reporting an improvement in clinical status.

As we follow patients over time, we again see that by 24 hours about 80 percent of Natrecor patients are feeling better, and by the end of therapy, about 90 percent of patients are reporting feeling better.

And the response rates for Natrecor are generally comparable to that being observed in the standard care treatment arm with the investigator's first choice, IV vasoactive agent.

In this study we also looked at symptoms of CHF, which is shown on the next slide, and we see the same pattern; that when we follow patients over six hours, 24 hours, and the end of therapy, patients receiving Natrecor had a continuous improvement in these symptoms over time, which was generally comparable to that being obtained with the IV vasoactive control agent.

Thus study 326 supports a role for Natrecor as an IV vasoactive agent for the short term

treatment of CHF. In this study we, again, saw a rapid improvement in global clinical status, and specific symptoms of CHF.

The response rates seen here were very similar to those obtained in study 325 for Natrecor patients there.

In addition as we followed patients over time, being treated primarily with Natrecor as the sole IV vasoactive agent, we see a continuous clinical improvement through 24 hours and the end of therapy.

So to conclude a summary of Natrecor's efficacy results, Natrecor has been shown to have beneficial effects on both hemodynamics and clinical status. With regard to hemodynamic, Natrecor has been studied in seven randomized double blind placebo controlled studies, and at each of these studies has reduced pulmonary capillary wedge pressure.

Highly statistically significant results were obtained for the primary efficacy endpoint of a reduction in wedge in both pivotal efficacy studies 311 and 325.

In addition, these studies have shown that

Natrecor has an overall beneficial hemodynamic profile characterized by reductions in pre-load and afterload, and increase in cardia index, and this is obtained without an increase in heart rate.

I have also shown you that Natrecor administration results in a rapid improvement in clinical status. Natrecor improves global clinical status when assessed either by the subjects themselves, or by their physician.

And Natrecor also improves specific system of CHF, such as dyspnea, when compared to placebo.

Thus, Natrecor has been shown to have the characteristics desirable for an IV vasoactive agent for the short term treatment of CHF with beneficial effects on both hemodynamics and clinical status.

The last topic I will discuss this morning is our recommendations regarding dosing. And as I mentioned, we are recommending that Natrecor be administered as a fixed dose infusion of a dose of 0.015 micrograms per kilogram per minute without a preceding loading bolus.

And I will now review the rationale for

each of those recommendations.

First, with regard to the doses, as I've mentioned, Natrecor has been studied over a wide dose range, ranging from .003 to .1 micrograms per kilogram per minute. But doses in the range of 015 to 03 appear to be the optimal dose range for patients with CHF, and therefore these two doses were studied extensively in the phase III program.

And both of these doses were efficacious by all of the criteria assessed. Both doses achieved highly statistically significant effects on the primary efficacy endpoint of reduction in wedge pressure in both pivotal efficacy studies, 311 and 325.

Both doses have been shown to result in a reduction in pre-load and afterload, and an increase in cardiac index, in both studies 311 and 325.

Both doses resulted in improvements in global clinical status when compared to placebo, either when assessed by the subjects themselves, or by their physician. And both doses resulted in improvement in symptoms of CHF.

When you look at the effects of the two doses on clinical status and symptoms, you may have noticed, however, that the 03 dose did not seem to result in a more marked clinical response than did the 015 dose.

In addition Natrecor is accompanied by dose related reductions in blood pressure, which are greater at the 03 dose than the 015 dose.

We therefore feel that the 015 dose offers the optimal benefit risk profile with patients with decompensated CHF. And we therefore recommend that as the initial dose for patients.

Now, we are not ruling out the use of the higher dose in an individual patient who is receiving an infusion of the 015 dose, tolerating it well, but in whom a greater hemodynamic response is desired, the dose could be increased up to 03, but we would recommend that dose increases not be made more frequently than every three hours, to allow the peak hemodynamic effects of Natrecor to occur before further dose titration is undertaken.

I will now discuss the rationale for our

recommendation that Natrecor be administered without a loading bolus. And this is somewhat noteworthy, since we did use a small loading bolus in both our pivotal efficacy studies, as well as study 326.

Now, the loading bolus administered in those studies was very small, for the dose -- the infusion dose of 015 micrograms per kilogram per minute the loading bolus was .3 micrograms per kilogram.

Now, this is showing the results of study 305, which is a study in which individual bolus doses of Natrecor were administered to patients with CHF, and the effects on hemodynamics were followed for four hours.

You can see here that when a bolus dose of ten microgram per kilogram is administered, potent hemodynamic effects are obtained. A dose of 3 microgram per kilogram which was the lowest dose at which discernible hemodynamic effects were seen.

At doses of 1 microgram per kilogram or lower, these boluses did not result in discernible hemodynamic effects. Therefore the loading bolus

preceding the 015 infusion would have not been expected to have any discernible hemodynamic effects of its own.

Now, after completion of the phase III program, we went back and did a more detailed pharmacodynamic assessment of Natrecor pharmacodynamic profile. And we could see that adding that small loading bolus had not altered the pharmacodynamic profile. This is shown on the next slide.

Here we are comparing the effects of Natrecor on wedge pressure at two time points, one and a half, and three hours, in two studies. Study 306, a study in which a loading bolus was not used, and study 325, a study in which a loading bolus was used.

You can see that in both studies the effects on hemodynamics were quite similar, and the loading bolus did not appear to alter the pharmacodynamic profile of Natrecor.

Thus we feel that the use of the loading bolus did not significantly contribute to the efficacy profile of Natrecor. And we recommend dropping the use of the loading bolus to facilitate drug dosing,

and to avoid possible dosing errors that could result from the use of the loading bolus.

So, to conclude, the data I presented this morning demonstrates that Natrecor Nesiritide is an efficacious agent for the short term treatment of CHF, with beneficial effects on both hemodynamics and clinical status.

I would now be happy to answer any additional questions you might have with regard to the efficacy data.

CHAIRMAN PACKER: We will open the discussions with our primary review, Marv Konstam. Marv?

DR. KONSTAM: Thanks very much. I have questions in a couple of different regards. I want to start about the population, about the nature of the population, and particularly just try to get a clearer view about who are these patients, particularly in study 325, where I think you made the point that you tried to enroll patients who were acutely decompensated, requiring some kind of intravenous therapy.

What more can you tell us, you know, to sort of clarify that? Because all I see at this point is just that sentence, and I just wonder how do we know they are really decompensated clinically?

DR. ALLGREN: Well, these patients were basically identified by the investigators. I think the important point to note is that these were not designed as basically pharmacology studies, in which patients being seen in a CHF clinic would volunteer for study participation.

These are really a study of patients who had developed decompensated CHF were being admitted to the hospital, would have been put on Dobutamine or Milrinone, or some other agent, but were identified for the study, and therefore randomized into the Natrecor study.

DR. KONSTAM: Is that different in 311? In 311 --

DR. ALLGREN: A little bit. I think the patients in 311 were more of a mixture. There could have been some acutely decompensated patients there, but they also would include some patients who are more

chronically decompensated being followed in the clinic who might have been admitted for study participation.

DR. KONSTAM: So in 311 you could admit a patient specifically for the study, they were not necessarily admitted to the hospital for decompensation of heart failure?

DR. ALLGREN: Right.

DR. KONSTAM: Whereas in 325 they all were admitted?

DR. ALLGREN: 325 and 326, both, it was aimed at decompensated patients requiring admission.

DR. KONSTAM: Do you have -- I was thinking about how to sort of show this to us about how sick they were, and everything. Do you know something about the duration between the time that they were admitted, and the time that they were enrolled in the study, do you have any information about that?

DR. ALLGREN: I think it was a mean of about one day.

DR. KONSTAM: One day?

DR. ALLGREN: Yes.

DR. KONSTAM: Well, that causes me pause because, I mean it was one day --

DR. ALLGREN: Well, in study 325 patients could have already been in-house, receiving IV vasoactive agents.

DR. KONSTAM: In 325?

DR. ALLGREN: Right, right. So there were actually some patients in that study who could have been getting an IV vasoactive agent for a few days, and then --

DR. KONSTAM: And then it would have been stopped for the study?

DR. ALLGREN: Right, right.

DR. KONSTAM: Well, I mean I -- you know, let me -- I don't want to press this too hard, because I think this is really hard, you know, to do these types of careful studies in patients who are acutely decompensated. I suspect you did the best job you could.

I just, you know, I was just trying to picture exactly how decompensated they really were at that time, and whether -- I mean, I guess if they were

in-house for about a day, and they may or may not have been on IV diuretics, I guess it is a little bit different picture than, you know, they are in there, they are acutely decompensated, the doctors are racing in to give them IV drugs, and we are going to randomize them.

And I guess that is what I'm struggling with. I'm not sure what to do with that, but I'm still struggling with it.

DR. ALLGREN: Our intent was to enroll acutely decompensated patients and from our conversations with investigators, that is our impression of what was occurring in those studies.

DR. KONSTAM: Okay. Now, I just wanted to ask you about dose response, and particularly it looks a little different than 311 and 325, wherein 311, you know, I don't see a clear dose response between the .015 and .03. In fact, depending on how you slice it, and the different graphs, it looks like it is actually the other way, it looks like -- the two doses look either equivalent, or in fact the 015 looks better.

DR. ALLGREN: Yes, we noticed that as

well. We don't have an explanation for that, that is what was observed in that study. I would just note that that was specific to that one study, and in other studies we have seen a clearer dose response in that dose range, and study 325, as you mentioned, there was a clear dose response, and in study 307, which I presented earlier, there was a clear dose response between the 01 and the 03 doses.

DR. KONSTAM: Well, I guess this is going to come up, you know, in issues of dosing, you know, and cost benefit analysis with regard to safety. So I'm not quite clear about whether or not you get added benefit from the .03 dose or not.

Okay. I would like to ask about, you know, just issues of pharmacodynamics, on both sides, that is rate of onset, and rate of offset. And first with regard to onset, it seems to me, looking at all the graphs, that it takes several hours to reach the peak effect in terms of pulmonary capillary wedge pressure.

DR. ALLGREN: About three to six hours.

DR. KONSTAM: Three to six hours. Can you

explain that?

DR. ALLGREN: I think there is a lag between the pharmacodynamic responses with regard to effects on wedge pressure and the plasma levels.

DR. KONSTAM: Any idea why that might be? I guess it is not that important for us to know why.

DR. ALLGREN: Perhaps it has something to do with second messenger system activation.

DR. KONSTAM: Right. Well I guess it is going to raise an issue with regard to how to use this drug, and is the same thing true with regard to blood pressure effects? I'm not sure I've seen that graph.

DR. ALLGREN: Yes, that is going to be discussed in more detail by Dr. Horton during the safety presentation, but there is a similar curve with regard to the time effect.

DR. KONSTAM: In terms it takes 3 to 6 hours to reach the maximum effect on blood pressure?

DR. ALLGREN: Yes.

DR. KONSTAM: Okay. Now, I want to ask about the duration of effect. You said that it is sustained over 24 hours, and I guess that is a

subjective call.

I'm looking back at your slide, I have it labeled number 21, which shows the plots for hemodynamics for 311. And I was just trying to do some quick extrapolation of the time points.

It looks, to my eye, it looks different at the different doses, and I'm not sure -- I guess, again, a subjective call. The .015 dose looks better, again, than the .03 dose. I mean, the .03 dose, for example, I've got -- it looks like it is about a 27 or so percent reduction at six hours, and then at 24 hours you are down to about, I don't know, 13 percent or so, reduction from baseline?

DR. ALLGREN: Yes, there are a couple of things worth noting about this, or remembering about this, since trying to look at the effects over 24 hours is actually a little more complicated than you might think.

DR. KONSTAM: Right.

DR. ALLGREN: First of all we have to remember that there are some dose modifications going on in this study. About a quarter of the patients in

the 015 and 03 dose groups reduced the dose by the time of the 24 hour measurement, and half of the patients in the 06 dose group.

So that would contribute to somewhat of a trend of these curves appearing to taper off at the 24 hour time point.

DR. KONSTAM: Well, I guess, you know, for what it is worth, I guess that the -- one of the questions to ask is, is there a sustained effect, yes or no. And I'm still not -- I mean, it seems -- my read quick, is that there is a sustained effect, but I'm not sure that we are not beginning to lose it at 24 hours.

DR. ALLGREN: Yes, I think if you look at these curves, I mean, particularly for the 015, that you can see that it is fairly stable from the 10 hour to the 24 hour time point.

And, in particular, if you look at when the drug infusion is discontinued at 24 hours, you can see a rapid return of hemodynamics to baseline, which is really suggesting that there is active effects of

the drug on hemodynamics through that time point.

DR. KONSTAM: Yes, okay. Let's see, I guess my last set of questions just relates to the symptom assessment, and global assessment of the patients.

And I have some question about the blinded nature of this -- of the analysis. And the independence of the analysis between the physician's analysis and the patient's assessment.

And this has been raised by the medical reviewer. And I guess there are a couple of points of potential unblindedness of the analysis. One is -- well, I guess a couple of questions. One is -- well, let me ask this.

To what extent, with regard to the patient assessment, was that a questionnaire that the patient filled out, or was that something that the patient and the physician did together?

DR. ALLGREN: The patient would usually be asked how they were feeling, and to rate it according to that five category scale. That assessment might have been done by one of the sub-investigators or

study coordinator.

DR. KONSTAM: All right, so it wasn't just a questionnaire that the patient filled out and handed in. There was interplay between the doctor --

DR. ALLGREN: Different sites might have done that differently, but my impression in general was that they were asked to respond to that question.

DR. KONSTAM: With regard to that and also the physician assessment, were the physicians who were doing these assessments, and the physicians in the study coordinators who were helping, working with the patients, were they aware of the hemodynamic responses?

DR. ALLGREN: Yes, they would have been.

DR. KONSTAM: Because I was thinking about that graph you showed. I was impressed, personally, with that graph you showed between the correlation between wedge pressure and clinical scores.

But I'm not sure I've seen data quite like that before, which are good. But I wonder about the independence of those two indicators if, in fact, the physicians filling that out knew the hemodynamic

response at the time they were filling it out.

DR. ALLGREN: One thing to keep in mind is that very similar response rates were seen in study 326, where most patients did not have a Swan-Ganz catheter.

DR. KONSTAM: Right. That is a good point, although there we don't have a control -- we don't have a placebo group, so that is the -- I mean, that is not really something you are showing for efficacy, I guess, because we don't have a placebo group.

But, I mean, I agree. I mean, it all looks consistent, but I guess there is still a little bit of a question in my mind about that.

And, also, my last question about that relates to the timing of the unblind, and for study 325. The timing of the unblinding relative to the physician assessment. I mean, is it possible that some of these assessments were done after the investigator actually knew what drug the patient was on?

DR. ALLGREN: The way it was supposed to

have been done, all these assessments should have been done before the six hour unblinding, which was actually done by a computerized unblinding system, that the investigator would call document that the assessments had been done, and then they would be given the unblinding code.

In some cases, when we looked at source documents, the time of that unblinding was after the time of the randomization clock unblinding in a few of the patients. We've done analysis which both include those patients, and exclude those patients, and in essence get some of the results.

DR. KONSTAM: How many -- you say in a few of the patients it was --

DR. ALLGREN: Maybe about 20 percent have a clock time that doesn't line up with the unblinding clock time. But you also have to keep in mind that one thing we found was that there was differences in watch times between the investigators watch at the site and the clock time at the central unblinding time. So some of these times could be a few minutes apart.

I don't know that that necessarily means the investigators were actually unblinded at the time.

DR. KONSTAM: Okay, thanks, those are my questions.

CHAIRMAN PACKER: Marv, let me see, I think you've listed at least six categories of issues, patient population, hemodynamics, dose response, time of onset, persistence of effect, and symptoms.

And I would like for the Committee to focus on each of these, and at least have focused discussions on these. It doesn't really matter what order they are in.

And let me first just see if we can do that. So let's talk about the patient population first. Does anyone have any specific comments about the type of patients that were enrolled in the trials?

Tom?

DR. GRABOYS: Part of this is just going to be for you to elicit on the entry. Now, you said the mean time for entry was one day on those patients when they were enrolled?

DR. ALLGREN: In study 325. But as I

mentioned, that would span patients who had been in the hospital already on other vasoactive agents versus patients being directly admitted from the emergency room.

DR. GRABOYS: And patients who were entered in the placebo limb?

DR. ALLGREN: Pardon me?

DR. GRABOYS: The patients who were entered in the placebo, also they were mean time of a day?

DR. ALLGREN: Right. The study was initially double blinded, so at enrollment they wouldn't have known which dose group they were in.

DR. GRABOYS: And then they were enrolled, and for six hours they essentially were on no therapy whatsoever?

DR. ALLGREN: Right.

DR. GRABOYS: I mean, they didn't receive oxygen, they didn't get any diuretics?

DR. ALLGREN: No, they could have gotten supplemental oxygen. Diuretics and other vasoactive agents were supposed to have been withheld for that

six hour period, the first six hour period.

DR. GRABOYS: I'm sorry, were supposed to be withheld, or were actually withheld?

DR. ALLGREN: They were withheld with the exception of maybe three to five patients who did receive diuretics, or an IV vasoactive agent.

DR. GRABOYS: Three to five who were on placebo?

DR. ALLGREN: No, across the groups.

DR. GRABOYS: Okay.

CHAIRMAN PACKER: Any other questions relating to -- Bill?

DR. ABRAHAM: Yes, let me comment, as an investigator --

CHAIRMAN PACKER: You have to say your whole name.

DR. ABRAHAM: I'm sorry, Bill Abraham from the University of Cincinnati.

Let me just comment on patient selection or demographics as an investigator in these studies. And I think as you all appreciated, and as Marv has already commented on, these are difficult studies to

do, but you want to try to find the right patients.

And, in fact, these patients had a requirement in 325 and 326 for IV vasoactive medications, at least in the judgement of the investigator.

In the case of protocol 325 there was hemodynamic confirmation of decompensated with requirements for elevated wedge pressures and reduced cardiac outputs.

And, in fact, if you look at the average baseline numbers, this is a moderately sick group of decompensated heart failure patients with wedge pressures around 25 to 30, and cardia indexes around 1.7 or 1.8.

In fact patients with cariogenic shock are not included in this study. Patients who could not tolerate six hours without acute therapy are not included in these studies. But, in fact, I don't think that is the right kind of patient for which this drug is intended anyway.

And so the group of patients who require more than oral therapy, but less than acute

intravenous pressors seem to be the patients included in these studies.

DR. KONSTAM: Bill, I don't want to belabor the point, but I'm not, with regard to the hemodynamics, if I read the hemodynamic entry criteria, they were if anything slightly more liberal in 325 than they were in 311.

So I'm not sure that the hemodynamics, I mean, in terms of characterizing what patients, I don't think that the hemodynamics really help that much, to my read.

CHAIRMAN PACKER: Let me see. Bill, you may need to come back up. Ileana?

DR. PIÑA: I noticed, and I'm wondering why in the selection criteria for 325 you did not have an ejection fraction, were you concerned that you would ever pick up some of the preserved systolic function patients with decompensated heart failure?

DR. ALLGREN: Right. In both studies 325 and 326 there was not a restriction on ejection fraction, and that was based on the fact that we assumed that in actual clinical use patients baseline

ejection fraction might not be known in all cases, and therefore we wanted to gain safety experience with a broad population of patients that didn't have a lot of restrictions on their enrollment criteria.

DR. PIÑA: Did we see, or maybe I missed it, do you have the ejection fractions at all on 325?

DR. ALLGREN: It was a mean of 21 percent, I believe.

DR. PIÑA: So you did pick up primarily the systolic dysfunction?

DR. ALLGREN: Uh hum.

DR. PIÑA: My other question was on the diuretic use.

CHAIRMAN PACKER: We are going to go around again. I just want to focus on patient population first. Let's just focus discussion, then move on to the next issues. I'm sorry, diuretic use as identifier for patients? Oh, okay.

Joan?

DR. LINDENFELD: Can you just give me some idea of the total amount of diuretic given in the 24 hours before entry into 325?

DR. ALLGREN: Unfortunately no. I don't have that off the top of my head.

DR. LINDENFELD: So we don't know if there is a difference in how much diuresis the patients had between groups?

DR. ALLGREN: Diuresis in --

DR. LINDENFELD: A total amount.

DR. ALLGREN: Are you interested in -- you are saying Natrecor's diuretic properties, or are you saying --

DR. LINDENFELD: I'm interested in knowing how many of the patients in the placebo versus the Natrecor group had diuresis or substantial diuresis, or diuretics in the 24 hours preceding entry.

DR. ALLGREN: We didn't collect urine output prior to study enrollment.

DR. LINDENFELD: Just in understanding the patients, these patients were in the hospital for the 24 hours. They all -- did they all get diuretics, they were all acutely decompensated?

DR. ALLGREN: Which study are you referring to?

DR. LINDENFELD: 325, I'm sorry.

DR. ALLGREN: Well, as I mentioned, that is a mixture of patients, they wouldn't have all necessarily been in hospital for a day prior to getting Natrecor. They may have received, if they were already in house they may have already received diuretics, or might have gotten diuresis in the emergency room.

DR. LINDENFELD: But how about the ones that were in hospital, did they all get diuretics prior to entry? I'm just trying to figure out if these are really acutely decompensated.

DR. ALLGREN: My presumption wouldn't be that --

DR. LINDENFELD: Because if they didn't I would have some questions about that.

DR. ALLGREN: -- they would have been, but I don't know the answer to that.

CHAIRMAN PACKER: Can we just follow up on that for a moment? I think Bill mentioned the fact that one of the distinguishing features of 325, as opposed to 311 was the fact that patients with 325,

the entry criteria, where the need for IV therapy for decompensated heart failure, is that right Bill?

To me that means that a physician, in fact, intended in his or her clinical judgement thought the patient needed IV therapy, they probably would have given the IV therapy for clinical need, and then went through the process of enrolling the patients into a trial, which takes some time; you have to get informed consent, and do all the things that you need to do.

My marker of how sick patients might be under those circumstances was to find out how many patients got an IV diuretic within 24 hours, because that would indicate that the physician thought that an IV drug was needed, at least it would be highly correlated with some clinical decompensation.

I think that would be more sensitive than hemodynamics. How many people in 325 got an IV diuretic within 24 hours of enrollment?

DR. ALLGREN: I can show you the percentage of patients who got any sort of diuretic. I don't have IV diuretics broken down.

CHAIRMAN PACKER: That really wouldn't help very much. Anyway, think about getting that information as an indicator of the confirmation of the entry criteria that you specified for 325.

Second is, any patients with acute MI start in your clinical trials?

DR. ALLGREN: No, patients were excluded if they had had an acute MI within the preceding 48 hours.

CHAIRMAN PACKER: In previous discussions of this Committee, there has been a general recognition that patients with acute MI formed a significant proportion of the patients that are likely to develop acute decompensated heart failure.

And therefore we had specifically said, in previous discussions, even discussions as far back as more than a decade ago, that such patients should be evaluated in the clinical program.

Did you consider the inclusion of such patients, or the evaluation of such patients?

DR. ALLGREN: No, we were really focusing our program on the set of patients that were not

having acute MIs.

CHAIRMAN PACKER: So you think patients with acute MIs really are not candidates for this drug?

DR. ALLGREN: I wouldn't say that they would never be candidates for the drug, but we were really focusing on patients not in the acute MI setting, but patients who were presenting with decompensated CHF.

I would point out that over half of the patients we were looking at did have a history of ischemic cardiomyopathy. So we were studying patients with coronary artery disease, but not patients with acute MI.

DR. LINDENFELD: How many of the patients had angina, did any?

DR. ALLGREN: During the study?

DR. LINDENFELD: No, I mean, just any history of exertional angina along with the --

DR. ALLGREN: I don't, offhand, know that.

CHAIRMAN PACKER: Jay?

DR. COHN: I am sorry I missed the

presentation, but I have been through all of your data. I guess back to the issue of the patients you've included here, I was kind of surprised to, in the co-therapy analysis of the trial, discover that only about -- I think it was about 60 or 70 percent of the patients had been on diuretics, and even a smaller percentage on ace inhibitors, which strikes me as somewhat unusual for this kind of a population.

And I think the point Milton has raised is, concerns me, in that there are really two reasons why patients need to be treated intravenously for a high pulmonary capillary wedge pressure in the setting of chronic heart failure.

One, of course, if they've had an ischemic event, and that group has been excluded. The other is, usually, if the patients have accumulated fluid, and have an expanded intravascular volume, and the treatment for that is usually a breadth of diuretic therapy.

So the fact that these studies have been done in patients who haven't been aggressively treated with diuretics, at least a large fraction of them,

makes me wonder whether this is a patient population in whom this really is the appropriate approach to therapy, or whether aggressive diuresis would have been a more prudent way to initiate therapy.

Can you kind of address the co-therapy issue, because it is very hard to sort it out.

DR. ABRAHAM: A couple of points to be made here. One, I believe that the data that you are referring to looks at concomitant drug therapy, some of which was protocol driven.

For example, in 311 standard therapies for heart failure were withheld during 24 hours of study. So I think that brings down the percentages of patients that were treated with a concomitant medications that we would consider appropriate for these patients.

What we don't have available, in particular, in answer to the IV diuretic patient, is what did these patients receive, particularly in regard to IV diuretics prior to study enrollment.

But I think there are a couple of things which help characterize the patient population. One

is that in study 325 I think about 77 percent of these patients were already hospitalized for the treatment of decompensated heart failure at the time of enrollment in the study. Only 23 percent were admitted, and the admitted more or less directly into the study.

In addition the average wedge pressure, and I would agree that we can't hang our hat on hemodynamics alone, but even though some of these patients had already had substantial therapy including IV vasoactive medications prior to enrollment in the study, the average baseline pulmonary capillary wedge pressure was 28 millimeters of mercury.

I think we would all agree that that is still not even within the range of what we would consider to be reasonably well compensated.

So, again, I don't think this is a group of extremists, or patients with severely decompensated heart failure, cariogenic shock. On the other hand I think it does represent a good sample of patients who we wed typically admit to the hospital for these forms of intravenous vasoactive therapy.

DR. COHN: In some instances is the elevated wedge pressure a manifestation of having withdraw prior treatment six or twelve hours prior to the study? I mean, this could well be.

I think the troubling thing here is that the studies have been designed to demonstrate the efficacy of the drug, and there seems to be little question that the drug has efficacy. But they were not designed to tell me how to treat a patient.

And I think that is going to become the kind of sticking point here, is how do we translate this efficacy into a therapeutic regimen for a patient with severe heart failure.

CHAIRMAN PACKER: Ray?

DR. LIPICKY: You think that the information collected from the trials can't be applied to any other patient population in the patient population studied?

That is, you would expect that if someone had more severe heart failure, or had had the need for IV diuretics within the last 24 hours, that Natrecor would not have had the effect that it had?

CHAIRMAN PACKER: I think it is two separate issues. One is an issue of what are the effects of the drug, and are they going to be the same, regardless of the patient population.

And the second is, what is the safety of the drug, and would in fact it be the same regardless of the patient population. Two separate and distinct issues.

I think that others can comment as to which one of those issues is most pertinent to them. In my own view, safety is a big component of the total experience of the drug.

And we have specifically emphasized, in the past, going back quite some time, that acute ischemic states represents a big proportion of the patients presenting with an acute heart failure syndrome.

And that the safety profile of any given drug in acute ischemic states could differ substantially from the safety profile in more chronic conditions. I'm expressing my own point of view, but it is a point of view which the Committee has actually

emphasized now going back to 1987.

Marvin, Jay, do you have any other comments on the efficacy side, as well?

DR. KONSTAM: Well, I think we will probably have an expanded discussion about this later. I mean, I just want to say, for my part, I think it is important to characterize the populations studied. I think that Milton and Jay's points are that ideally if we are going to talk about using this drug for decompensated patients, ideally would like that.

But I have to say, I mean, I will just add an editorial on a practical note. I don't think we've ever seen a study like that, you know, in that population in a well controlled randomized format. I think it is very, very hard to do.

And I think, so that when we come back and decide about all this, I mean, to me this is just a matter at this point, of clearly knowing what is the population studied and how to apply that.

CHAIRMAN PACKER: Jay, do you have anything to add?

DR. COHN: Well, I think we will come back

to these issues later on, because they are fundamental to decision on the practical use of the drug.

CHAIRMAN PACKER: Okay. Bill, brief.

DR. ABRAHAM: Yes, if we could just put up backup slide 267, because I think it answers, to some extent, Jay's concern about how to use this drug in a real world population. This was the real world study, protocol 326.

And here you can see the medications used not only during Natrecor infusion, but before study. And you will see here that a much higher percentage of these patients who, by and large, were admitted to the hospital, and directly into study, as opposed to 325, which had a higher representation of already hospitalized patients, that there is a much higher use of typical medicines that you would expect to see, such as diuretic therapy.

I'm sorry that we do not have this broken down on the basis of intravenous versus oral diuretic therapy. But, again, this gives you some flavor. These patients are predominantly treated with Digoxin, diuretics, and an ace inhibitor. There is a high

prevalence of use of non-intravenous nitrates, as well, in this group.

CHAIRMAN PACKER: Bill, before -- can you just comment on the lack of data on acute MI?

DR. ABRAHAM: You know, quite honestly, I think it is just, you know, a way of playing it safe in a drug development program.

CHAIRMAN PACKER: That, actually, is the problem.

DR. ABRAHAM: Yes.

CHAIRMAN PACKER: Okay. Let's go on to the next subtopic, which is hemodynamics. And I guess in order to do that one should include anything at all about hemodynamics dose response, time of onset, persistence of effect.

Ileana, why don't you begin?

DR. PIÑA: This is a question sort of similar to one of Marvin's observations. In your 325 I noticed that the lower dose, the .015 gave a more profound drop in systemic blood pressure than the .03.

DR. ALLGREN: I think that is not actually the case if you were to look at percent decrease. I

think that is partly -- if we could have slide 20?

This is actually plotting observed blood pressures. And if you look at the top right panel, the systolic blood pressure effects, the 015 dose is shown in yellow, and it is lower. But they are starting lower, those set of patients are just all -- this whole curve is beginning lower, if you look at the percent change, it is actually a fairly small percent change. The 03 dose is having a larger percent change from baseline.

And, again, Dr. Horton will be specifically discussing these effects on blood pressure in her safety presentation, and she has a graph there that shows this better.

CHAIRMAN PACKER: Anything else on hemodynamics from anyone? Joan?

DR. LINDENFELD: This probably isn't exactly hemodynamics, but can you give us the starting BU in creatinine and sodiums in these patients, do we have any data on that, at say zero and six hours?

CHAIRMAN PACKER: Joan, could you say that again? I'm sorry.

DR. LINDENFELD: BU in creatinine sodium. Baseline BU in creatinine, I guess that fits in here.

DR. ALLGREN: In study 325 it was in the range of around 1.2. I mean study 326 it was around 1.2.

DR. LINDENFELD: Serum sodium?

DR. ALLGREN: I don't, offhand, remember.

DR. LINDENFELD: It just would be nice at some point to see that at zero and six hours in the two studies.

DR. ALLGREN: We don't have serum sodium at zero and six hours.

DR. LINDENFELD: At baseline?

DR. ALLGREN: Yes, we can find baseline. But I would just mention that in general we did follow serum sodium throughout these studies, and there did not seem to be an effect of Natrecor on serum sodium.

CHAIRMAN PACKER: Let me just ask Lem to comment on a couple of issues. First, Lem, the sponsor was very careful in their presentation in terms of presenting all of the ways one could analyze the primary endpoint of pulmonary capillary wedge

pressure.

And they had specified -- the protocol specified analysis was actually an analysis that included only, for example, in study 311 only about 80 of the 103 patients. The FDA actually asked for some additional analysis.

Can you comment on the relative weight one would put on a per protocol specified analysis that only applied to a subgroup, or the more comprehensive analysis, more intention to treat all inclusive, or that wasn't protocol specified.

DR. MOYE: I would like to postpone my direct response to that for about ten seconds, just to say that I think that your fine presentation this morning was undermined a little bit by the slides you showed for the global assessment of clinical status, only because there are no standard error bars on those.

And so we look at these bars, and it looks like some go down and some go up. But without being able to factor in what the variability of those estimates are, those are really uninterpretable for

us.

I also want to start with an assertion that gets into the question that Milt directly asked me, and that is, the protocol really is preeminent.

It is, perhaps, unfair to say that the protocol is the bible of the study, but I think it is fair to say that the protocol is the rule book of the study. It is the set of principles instead of precepts that the investigators agree upon after vigorous debate, sometimes, after vibrant discussion.

And the reason these issues are so intensely debated is because once decided upon they must be fixed. And let me just tell you for a moment why they must be fixed.

There are two sources of variability in experiments. One source is sampling variability, and sampling variability gets to the notion that we, as investigators, have to make a compromise.

We would study everybody in the world with heart failure if we could. Of course we cannot, so we compromise. We give up studying the entire population, and we take a sample.

The compromise is that since Joan's sample will be different than my sample, and have different subjects with different life experiences, she will get different numbers than I will, that is called sampling variability.

Now, it has taken us statisticians about two hundred years to figure out what to do with sampling variability. I mean, I don't say that apologetically, or unapologetically, it has just taken that long to figure this out.

And we now agree what you do with sampling variability. However, the other source of variability is a source that we know that we can't really -- we don't know what to do with, frankly.

And that is the variability that comes from the inexact execution of a protocol. Sampling variability we know how to fold into a test statistic. But once the rules of the trial themselves become variable, they become contaminated with variability, we don't know what to do with that.

In some sense the protocol -- the sample is only good if it allows us to view clearly what is

going on in the population. The lens is the protocol. And once that protocol becomes variable, once it becomes questionable, the lens we have is blurred, it becomes distorted, and we are not really sure to what degree we can see what is going on in the population.

Now, in all fairness to the investigators, although they can be visionary, they are not omniscient, they don't have perfect vision, and they can't envision everything that is going to happen during the course of an experiment.

Now, there are some who would argue that a large effect size can overshadow, and adumbrate the variabilities in protocol execution. Part of our job today, I think, is going to be to decide whether small P values, in fact, can cover a host of methodologic things, or methodologic flaws.

We have issues of the -- of randomization procedure, and also issues of the analysis plans. I have one question, in particular, about the randomization.

I think it is stated in the description of one of the studies, is that there were patients who

were -- who were randomized to the trial, but who were not accepted into the trial, because they didn't meet exclusion criteria.

Well, to me this induces a terrible confusion, because from my point of view, when you randomize a patient into the study, you are bound to that patient, you are joined to that patient.

And whatever happens subsequent to the randomization, that patient really needs to be included in the analysis. So I guess my point -- my experience has been that patients who don't meet exclusion or inclusion criteria aren't randomized. But once you randomize these patients, then you really are bound to include them.

I think we need to hear a little bit more about the difference between the protocol specified analysis, and the intent to treat analysis. Intent to treat analysis is, I think, the standard that is used. And it is the standard because it leads to an unbiased attribution of effect.

The investigators pay a price for that unbiased attribution, because it winds up being a more

conservative analysis. But the clarity of attribution is more important, I think, than is the liberal interpretation of results.

So I hope that you can comment upon those. I guess I would just summarize and say that it seems to me that there is a critical mass, or protocol questions that can overshadow even the smallest P value. So this is a question of great concern to me.

DR. ALLGREN: Yes, we could walk through a couple of these issues, if I can have slide 123.

Now, we presented an intent to treat carry forward analysis. This was an analysis methodology that Dr. Temple had recommended to us. And this just summarizes the main facets of this analysis. It included all enrolled subjects, analyzed them according to the treatment group of randomization, and if a value was missing at the three hour time point, a value was carried forward from a previous on-drug period, or baseline, in this initial analysis.

Now, the second -- pardon me?

DR. MOYE: Excuse me, that first circle

with the three bullets, now, was that the protocol analysis, or was that the --

DR. ALLGREN: No, that is the one that was recommended to us by Dr. Temple. The one on the bottom is the protocol specified analysis.

The objective, the primary objective of this study was aimed at looking at the dose response characteristics of the drug. So the primary analysis was aimed at subjects that stayed on the correct drug of randomization through the three hour assessment time point.

So this excluded subjects with dosing errors, or dosing modifications that occurred before the three hour assessment. And, also, in order to be included in the assessment, the wedge had to be taken at three hours plus or minus 90 minutes.

Now, on the next slide, slide 124, this reviews the reconciliation of sample sizes between these two analyses. So all enrolled subjects are included in the intent to treat analyses. In the bottom you can see the patients that are excluded from the invaluable at three hour analysis, and this is

primarily because of dosing errors, or dose modifications. And in three cases wedge pressure observation is missing from the three hour time point.

DR. MOYE: Can you say just a word on why you chose not to do the intent to treat analysis as a protocol analysis?

DR. ALLGREN: At the time we were designing this protocol, as I mentioned, we were very interested in looking at the dose response characteristics of the drug, so the study was designed with that in mind, really focusing on subjects who completed the intended dose through the evaluation period.

DR. MOYE: And, now, how can you justify the fact that you randomized patients, but you don't consider them in the protocol analysis?

DR. ALLGREN: Well, that is a separate issue which we can go through in a moment. But to just briefly describe it, the protocol specified that the way the randomization would work is that when a likely patient was identified, in order to be sure that study drug was available to the physician at the

time that the patient was ready to be dosed, the investigator would notify the pharmacist, and they would consult the randomization code, and mix up study drug, and then they would send it to the floor. It is obviously in a double blinded, marked in a double blinded manner.

So the investigator is not aware of what drug they are getting, so that could not bias subsequent decisions as to whether or not to enroll a patient.

The physician would then insert the Swan-Ganz catheter and confirm eligibility. And the main reason why patients did not proceed with the study would be that once the Swan was put in the patient did not meet the hemodynamic inclusion criteria.

But if the patient met study criteria, then they would proceed with dosing, and at that point in time they would be considered enrolled.

We did analysis, including those patients, and I can come back to that. But let's just first finish looking at the comparison of these two analyses, the intent to treat, and the evaluable at

three hours.

Because if we look at slide 125, you can actually see that the results obtained here in these two analyses are very similar. This is the results of the mean change on wedge in the two analyses, and you can see they both achieved highly statistically significant results, both for the overall comparison, and individual pair wise comparisons.

CHAIRMAN PACKER: Lem?

DR. LINDENFELD: Can you just go back to the previous slide, help me for a second? So just, once again, I'm probably missing something here. But explain to me how all 29 placebo patients were evaluable, but 6 and 9 of the 2 dosing were not; what happened there? Could you just explain to me how --

DR. ALLGREN: In the second population --

DR. LINDENFELD: Where it says evaluable at hour 3.

DR. ALLGREN: Right. There were more patients in the -- those dose groups that had dosing errors, either overdose or underdosed, and then there were also more dose modifications in those patients,

none of those errors happened in placebo patients.

DR. KONSTAM: Wait, but the excluded line also? I'm sorry -- yes.

DR. LINDENFELD: But the placebo patients got placebo, and no errors were made there? But it was blinded.

DR. ALLGREN: Yes. Some of these dosing errors happened at the level of the pharmacist.

DR. KONSTAM: What about the excluded line, so many patients excluded?

DR. ALLGREN: That is the total -- it is summing up the four things underneath it.

DR. KONSTAM: O, I see.

DR. ALLGREN: So the excluded is representing patients who actually had a wedge measurement, but it wasn't used because they had a dosing error, or a dosing modification.

At the bottom line is people who actually had a missing wedge pressure at the three hour observation.

DR. KONSTAM: I guess Joan and I are both struck by the discrepancy between the placebo group

and the active drug group in this regard. I mean, it is striking. Not a single event like that in the placebo group, and all these events happening in the active drug group.

DR. ALLGREN: Well, I think that is not surprising given the fact that these dose modifications would be more likely to be made. These are after the patient is getting drugged, I mean, that these dosing modifications are being made. So people are --

DR. KONSTAM: You can make a million mistakes if you are not giving any drug, and it will not change the amount of drug you are giving.

CHAIRMAN PACKER: You can mistakes dosing placebo, because you don't know it is a mistake or not.

DR. LIPICKY: But you haven't changed the amount of drug you have administered.

DR. KONSTAM: Right, but they would have been included here in placebo, even though there was a dosing -- there might have been dosing errors or changes in the placebo group, but they would still be

in that 29?

DR. LIPICKY: The placebo group did not get any drug, but some of the patients who were getting drugs would have gotten a bigger dose than they were randomized to, or a smaller dose than they were randomized to.

DR. KONSTAM: But I don't understand. That could also have happened in the placebo group.

DR. LIPICKY: But they weren't getting any drug.

DR. KONSTAM: No, I understand that. But if that happened in the placebo group, would they still be in the 29 evaluable?

DR. LINDENFELD: If they had --

DR. KONSTAM: Dr. Lipicky is suggesting that if these dosing changes, or dosing errors had occurred in the placebo group, that you still kept them in at 29 evaluable patients.

DR. LINDENFELD: You are right, they probably would have been kept in, because it didn't result in a net change in the drug that the patient was actually getting. That is a good point.

DR. COHN: But I guess the issue is, were there any patients in the placebo group whose infusion was either terminated or reduced because of blood pressure falls, etcetera, even though they didn't get a different dosage of drugs, they may have had a change.

DR. ALLGREN: Not by the three hour time point. If we look at values through the 24 hours, yes, there are.

CHAIRMAN PACKER: Do we have clarification of this? I guess I'm a little bit confused. Notwithstanding the fact that an error of dosing of placebo doesn't have physiologic significance, but administratively, some of these are administrative dosing issues.

I think all of us would expect that you could make a mistake administering placebo just like you could make a mistake administering active drug, and therefore if you made a mistake administering placebo it should be recorded up there as a mistake, administering placebo.

DR. LIPICKY: But it was not.

CHAIRMAN PACKER: But were there? In other words, if this were done correctly --

DR. LIPICKY: No. I mean, what is correctly mean?

CHAIRMAN PACKER: Correctly means that the issue here is --

DR. LIPICKY: Well, no, no. Let me -- maybe we see this lot, and basically think it is okay. Well, I know you -- but if what you are interested in is, is dose X of the drug differentiable from dose Y of the drug, it seems unreasonable to include people in those comparisons that have gotten dose Z. That just doesn't seem rational.

Now, okay, so indeed I think it is reasonable to say I'm going to do an analysis of people who only got dose X, and only got dose Ye. And then I'm going to do an intent to treat, and see if that gives the same answer. If it does, I feel comfortable. If it does not, then you have to worry.

And that is all we are talking about here. Okay, is -- I want to know what the effects of dose X are. I don't want dose Z in that group. And I'll

worry about the interpretation I can make if an intent to treat analysis doesn't stack up the same way. Not P value-wise, but you know?

And then everything is honky dory if those two analyses agree with one another. And I'm comfortable with that, but I think that is what you are discussing, and the question is, how uncomfortable are you.

CHAIRMAN PACKER: There are a number of different issues. Why don't we just go around the table. We will go Lem and then Marv.

DR. MOYE: I understand the thrust of what you are saying, Ray. I get concerned when any of the analysis plans are data driven. I'm not sure whether the protocol said they were going to do both of these analyses, they were going to do an exclusionary analysis.

DR. LIPICKY: No, it did not. It said they were going to do an exclusionary analysis, and w told them they had to do the intent to treat analysis.

DR. MOYE: Okay. And therefore --

DR. LIPICKY: After they were through with

their analyses.

DR. MOYE: I see, okay. Well, then I guess I would just go on record as saying that I think it is a mistake to have a protocol whose analysis plan leads to, from my point of view, a massive number of patient exclusions.

I mean, I think you've got terrible problems with attribution of drug effect, to attribution of effect for the primary endpoint to the drug.

Now, to some degree you can try to salvage that by doing an intent to treat analysis in the end. But now if you are doing two analyses, what happens to your true type one error here?

DR. LIPICKY: That is the question Milton asked you at the very beginning, and now you've seen it and tell us.

DR. MOYE: Well, I think the effect is the following. The type one error is larger than -- now how much larger is the type one error is the subject of perhaps a protracted debate.

I would say, though, that again there is

a critical mass of these kinds of problems with an experiment that will overshadow the smallest type one errors, smallest nominal P value that comes from any one particular analysis or another.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: Well, I'm actually satisfied with what Ray said. I think the issue is the potential for bias resulting in excluding certain types of patients.

I think the point is if, for me, if it is confirmed by both analyses we are less worried.

CHAIRMAN PACKER: Let me just add, I just want to add my -- I think that there are two separate issues here. There is one issue is does it matter or not? The P values are very robust.

And although Lem has said that you can only hide a certain number of sins with small P values, we've seen a lot of NDA's hide an enormous number of sins in small P values. And, in fact, the blanket under which one could hide, since under small P values is really quite large.

DR. MOYE: It is as large or small as we

make it.

CHAIRMAN PACKER: But I think we can all be very comforted by the fact that regardless of how they do this analysis, the P value is very small. And if you correct it multiple times for all sorts of real or potential reasons for correction, my sense is it will withstand all sorts of re-analyses and scrutiny.

So that is not the issue. The only question that I wanted to raise was, it is very, very common to get people who don't do the protocol the way it is supposed to, because that is life.

One always feels a lot more comfortable if the number of people who don't do the protocol the way you are supposed to is equally distributed amongst the treatment groups.

And I get a little nervous if I see that the people who didn't do the protocol the way they were supposed to, especially when it doesn't have a lot to do with the drug action, but it has to do with administrative errors, is unequally distributed amongst the treatment groups.

That is that it should be as likely to

make a mistake formulating the infusion or dosing the infusion, or whatever, across all the treatment groups, because no one knows what the treatment assignments are.

So if one sees an unequal distribution of administrative issues or errors, one wonders whether there was any potential for unblinding. And I don't think that is what is going on here, let me specify that.

But when you see the numbers that Joan pointed out, you know, 29 and there is 7 missing, or 9 missing, whatever; and it could be that it is just presented in a misleading way.

But one would like to see mistakes being made equally across the treatment groups. I think that is the point, right?

DR. MOYE: Yes, no, the P value doesn't tell you anything about the degree to which those kinds of administrative errors confound the results. In fact, you could have -- one could imagine, again it did not happen here, but one can imagine administrative snafus that can be the explanation for

the small P value.

But because you have the small P value, the sense is that a small P value sanctions the result, and sanctions the attribution of effect. And that is not the case. The small P value tells you nothing about effect attribution here.

DR. LIPICKY: But, in fact, holler at me if I say something wrong, when the primary analysis is done for protocol, you know, we honor that. And then when we say, okay do an intent to treat also, I don't even look at the P value, I just look to see whether the results come out the same. And so this is not a P value discussion.

DR. MOYE: Right, right.

CHAIRMAN PACKER: Most of this is going to -- I'll just ask one question. There are some reasons for excluding that are drug specific, side effects, they had to reduce the dose, etcetera, etcetera.

Of the exclusions that have nothing to do with an action of a drug, but have to do with administrative errors, I don't have the slide that you had in front of you, but underdosing, overdosing,

things that are sort of the usual life issues in a clinical trial.

Were they equally distributed amongst the treatment groups? Did anyone make a mistake administering placebo?

DR. ALLGREN: No. Or not that we are aware of.

CHAIRMAN PACKER: I see.

DR. LIPICKY: How could that be? Everyone who got placebo got the right infusion rate, and it wasn't changed?

DR. ALLGREN: That we are aware of, but --

DR. LIPICKY: Well, then I'm worried now. I mean, I -- how can that be? I mean, somebody must have made a mistake.

DR. ALLGREN: Well, again, the dosing errors, if we could have slide 124 back?

Many of these, the bottom -- many of these here are due to dose modifications and terminations, which are actually for the most part related to decreases in blood pressure.

And then some of these have to do with

either randomization errors, or drug -- this is really the one that is directly related to drug preparation errors.

DR. KONSTAM: Just let me say, I mean, maybe you don't know whether they were administrative errors or not, in the placebo group. I mean, frankly, if you really knew that there were no administrative errors in the placebo group, and we would have to figure out exactly how many there are in the others; I quite frankly would challenge the blindedness of the study.

I mean, I think that that is a much bigger issue than the issue of what the right P value is here.

So, you know, I'm concerned about what you are saying. I'm wondering whether it is just not right, is that in fact there were administrative errors in the placebo group, but you just haven't counted them, or haven't --

DR. ALLGREN: Yes, I can't respond to that, I'm only aware of what is listed here.

DR. LIPICKY: Did someone have to put drug

into a vial?

DR. ALLGREN: It is D5W is the placebo.

DR. LIPICKY: And how did drug get into it?

CHAIRMAN PACKER: You have to come up and use the mikes, I'm sorry.

DR. ALLGREN: He was saying that the placebo is D5W.

DR. GROSSBAR: There was no placebo vial, the pharmacist just used D5W as placebo.

DR. LIPICKY: But then someone needed to put drug in.

DR. GROSSBAR: For the drug part there were serial dilutions done, so you diluted the vial, and then you took an aliquot from the vial and made a solution with D5W.

DR. LIPICKY: So then somebody knew that someone had not added anything to the D5W?

DR. GROSSBAR: The dilution was multiplied. If you were supposed to give someone .03, someone did the dilution twice, and they ended up getting .003. You couldn't do that with placebo,

because placebo simply meant sending down the bag of D5W unadulterated.

DR. LIPICKY: So somebody knew that the D5W bag had had nothing added to it?

DR. ALLGREN: The pharmacist knew.

DR. GROSSBAR: It would be hard for the pharmacist to make a mistake by simply taking a bag and labeling it. And that is what the placebo was, it wasn't a vial where you diluted the vial, and then transferred it into a bag. So it was different operation.

DR. COHN: But how did you find out that the errors were made, when was that decision made, that there had been an error?

DR. GROSSBAR: There was a monitor who monitored the pharmacy. You know, a clinical research associate who went, monitored the pharmacy and the procedures, and discovered that in these cases, these dilution errors had been made. This was several months after the patients had been treated.

DR. COHN: You are pretty confident that monitoring was possible --

DR. GROSSBAR: The monitor was blinded to the treatment assignment.

DR. COHN: And what did the monitor look at in order to determine --

DR. GROSSBAR: Pharmacy records.

DR. COHN: Just the records?

DR. GROSSBAR: Right.

DR. COHN: And the records might have been in error as well, I suppose. We really don't know whether an error --

DR. GROSSBAR: But you couldn't have made this error with the dextrose bag.

DR. COHN: I can understand that. I guess I'm just a little confused about how accurate --

DR. GROSSBAR: We can confirm it, we also confirm it with plasma concentrations of the BNP in the patients. So there is an independent confirmation that the patients received a much lower dose, or at least their blood levels were much lower than comparable patient's dose in that dose group.

DR. COHN: Is that what alerted you to go back and --

DR. GROSSBAR: No, that is not. We subsequently confirmed it.

DR. PIÑA: I get the sense that most of the dose modifications are at this higher dose, and the dose terminated at this higher dose. And it sounds like it may have been triggered by an adverse event?

DR. ALLGREN: Right.

DR. GROSSBAR: Excessive reduction in the wedge pressure or --

DR. PIÑA: Or hypotension.

DR. GROSSBAR: -- or excessive drop in the blood pressure.

CHAIRMAN PACKER: I actually think that your comments have, you know, given us much more comfort about this, because the way that -- I mean, one couldn't make mistakes sending a D5W bottle down without anything in it.

DR. KONSTAM: Just follow that for a second, though. But if you made an administrative error, therefore, you were -- would the investigator have known that in some of these cases that there was

an error, and therefore something had to change during the course of the trial? Is that what happened?

DR. ALLGREN: Not necessarily, no.

DR. KONSTAM: That didn't happen?

DR. ALLGREN: No, this was discovered with an independent auditor auditing the pharmacy to check drug distribution records.

DR. KONSTAM: Okay, I got it.

CHAIRMAN PACKER: Joan has reminded me to remind everyone that when they come to the microphone they have to identify themselves, and that was Dr. Elliott Grossbar, so we just want to make sure that the record reflects who said what at what point in time.

And, thanks, Joan, I will continue to make sure that people do that.

Anything else with respect to the hemodynamic effects of the drug? We are going to go into symptoms in just a moment.

Lem, did you have anything more that you wanted to address in terms of the intention to treat versus per protocol analyses?

DR. MOYE: No, I think my questions have been answered.

CHAIRMAN PACKER: Can I just ask the sponsor one other question?

In study 311 not on the pulmonary wedge pressure, but on many of the other hemodynamic variables, although there was statistical significance on cardiac output or index, or PA pressure, or RA pressure, or systemic vascular resistance at three hours, many of these effects were no longer statistically significant at 24 hours.

And although those were secondary variables, it does, I think as Marv brought up in his comments, shoot yes, at least by the shape of the line, and not necessarily, but perhaps related to the lack of statistical significance that some loss of effect is occurring between 3 hours and 24 hours.

That possibility is, I think, reinforced by comments made by the medical reviewer, that at least with respect to A&P, which is a naturietic peptide, some attenuation or tolerance development has been reported.

Certainly the actions of this peptide resemble, in some ways, the actions of nitroglycerin, for which tolerance is a significant issue.

And some of that tolerance development occurs with nitroglycerin in studies that have lasted for 48 hours.

Why did you choose 24 hours in your clinical trial design? Because if one really wanted to make sure that this was a different effect than nitroglycerin, which generally develops tolerance in 48 hours, or between 24 and 48 hours, one would have liked to have seen the effect persist at up to 48 hours in order to show that what is going on here is not an attenuation of effect, and is different than what may have been reported in the past with A&P or nitroglycerin.

DR. ALLGREN: Yes, we did not do a study which really looked beyond 24 hours. When we were designing study 311 we felt that was a reasonable design for the study, and was a reasonable time period to expect these patients who still had symptomatic CHF to really go without other interventions in the

placebo arm.

CHAIRMAN PACKER: But this was a real stable group of people.

DR. ALLGREN: Moderately stable. They still had symptomatic CHF, and even during the 24 hour dosing period, in the 24 hour dosing period 5 placebo patients had to drop out due to worsening CHF, which required intervention with an IV vasoactive agent. So they were fairly sick patients.

CHAIRMAN PACKER: Dan?

DR. RODEN: This is as good a time as any to talk about this. So, Milton, before you can talk about changes in pharmacodynamics you have to be sure that the lack of pharmacologic effect at 24 hours, as opposed to three hours is not just a pharmacokinetic phenomenon.

So I want to come back to the issue of the boluses. First of all, can we look at your slide 21?

DR. ALLGREN: Slide 21?

DR. RODEN: So do you have plasma concentration data that would parallel the cardiac index, or the PCW measurements, particularly at the

higher dose?

DR. ALLGREN: Yes, we did look at plasma BNP levels throughout the infusion, and looked at clearance over time, and we did not see a statistically significant change in --

DR. RODEN: No, I want to see the plasma concentrations that correspond to these pharmacologic effects. Do you have that graph?

DR. ALLGREN: I don't have a slide of plasma BNP levels at 24 hours.

DR. RODEN: At what point did the plasma concentrations peak? Did they peak at one hour, or do they peak at six hours? Because you have two peak pharmacologic effects there.

DR. ALLGREN: They, in essence, peak almost immediately.

DR. RODEN: Right, so I can understand why the wedge pressure might take a while to go down if natriuresis takes a while to be accomplished, and that sort of thing.

The cardia index I'm a little bit more troubled by, but the question I have relates to your

recommendation that despite the fact that all the trials, the pivotal trials use boluses, you are telling us that you don't think you need to use boluses, and don't want to use boluses.

I'm sure we will come back to the issue of the right dose after we've had the safety discussion. But it seems to me that I have difficulty buying into the idea that the regimen that has been tested is not the regimen that is being recommended.

So I'm trying to find out why it is that you don't want to use boluses. It seems to me that at least some of the pharmacologic effect you see here could well be bolus related.

DR. ALLGREN: Well, I don't think that is the case. We have looked at that. As I mentioned, the bolus being given was a very small bolus, which itself did not have a discernible hemodynamic effect.

DR. RODEN: But you really haven't shown us that, have you?

DR. ALLGREN: In slide --

DR. RODEN: No, no, I saw the data. I watched the data go by. But I still don't think you

can eliminate this as a bolus effect.

DR. ALLGREN: Well, we have done -- we both have looked at the data, which I showed you comparing study 306 and 325. We have also done some pharmacodynamic modeling, looking at what the effect of various size bolus doses would be on the overall pharmacodynamic curve of Natrecor.

And both of them, really, show similar results of not having --

DR. RODEN: A model doesn't help me at all.

DR. ALLGREN: Pardon me?

DR. RODEN: A modeling exercise doesn't help me at all. There are lots of people that are enamored of that, I'm not.

AUDIENCE: Let me stress that on this slide the data includes patients in whom dose adjustments were made. And those dose adjustments in fact were down titrations of infusion rate.

So between the 3 or 6 hour time points, and the 24 hour time points, some of the patients reflected in this data had a down titration in dose,

which may partially explain these effects.

Now, if we look at backup slide 141, which excludes these patients who have had down titrations in doses, here specifically looking at the placebo group, compared to the .015 group, you will see that the curve generally is relatively flat. There is a fairly prominent dip at 6 hours, but between 10 and 24 hours the curve is fairly flat.

And, again, I think we can infer something important from what happens after study discontinuation. And I think both of those observations support --

DR. RODEN: I would like to see the plasma concentrations that go with these data.

DR. LIPICKY: Do we have a plot on any of our pages of plasma concentration versus time that could be shown to Dr. Roden?

DR. RODEN: And I would also like to see cardia index that belongs to this data. Do you have the cardia index plot with this --

DR. ALLGREN: No, we don't have a slide of that.

DR. RODEN: With the higher doses. Because it was the cardia index that sort of made me think that there may be a bolus effect, right?

Well, while you are thinking about that, let me just ask one other related question. And that is, I think it was your backup slide 125, one of the ones you just showed us. Could we see that again?

So we are going to come back to this, but I just wanted to make sure that I saw this, because it went by kind of quickly. It looks to me like there is not much of a dose response curve there.

DR. ALLGREN: Yes. In this study the 06 dose consistently resulted in -- well, depending on the different hemodynamic parameters, you are right here looking at wedge, all three doses were resulting in fairly similar effects on mean change in wedge.

DR. RODEN: So one conclusion might be that even the .015 is at the top of the dose response curve and that, therefore, that might not be the appropriate starting dose?

DR. ALLGREN: In this particular study, as we discussed in study 325 there was more of a clear

dose response, and also in study 307. This was the one study which seemed to give us this somewhat flat dose response curve.

DR. RODEN: Well, I guess we will come back to the doses after we heard the safety presentation. But I just wanted to make sure that I saw those data again.

DR. LIPICKY: We also do not have a plot of time course. I'm embarrassed by that, but I guess nobody has a plot.

DR. RODEN: Well I guess maybe I would ask the Agency, should I be worried about the fact that the boluses are not used or reviewed?

DR. LIPICKY: Yes, you should, and I'm embarrassed we don't have plot of the time course of plasma concentration to show you, but we don't.

CHAIRMAN PACKER: Dr. Karkowsky?

DR. KARKOWSKY: We do have a time course of high bolus concentrations, in a little tab, there is a couple of studies there. By 90 minutes you can't see anything after the high dose -- well, after boluses of 5 micrograms and 10 micrograms they are

pretty much gone.

But as far as the plasma concentration with constant infusions the only place you would have got that is 311, and I haven't seen that.

DR. RODEN: I guess I just sort of make a philosophical comment, and that is that the pharmacologic effects of a bolus may not be necessarily directly related to the plasma concentration.

I mean, if you go and abruptly achieve a high concentration in a perturbed physiologic environment like heart failure, it may be that you sort of get a jump start on the hemodynamic effects that you are seeing.

And, therefore, what happens after an hour or two of a maintenance infusion may, in fact, be related in some way to the fact that there was a bolus given before, even a bolus whose pharmacologic effects are not absolutely apparent when you give them by themselves.

And that is, I guess, my concern. I mean, I'm just perturbed of the fact that you evaluated

bolus regimens, and yet you are telling us that you don't think you need them. It will clearly make marketing the drug easier.

Marketing will be easiest if you can say to every doctor, this is the dose to use, period. But that really flies in the face of what we understand about individual variability and drug responsiveness.

And that is a philosophical comment that doesn't require an answer.

DR. LIPICKY: It isn't so much philosophy, it is a real comment, and we will have that data, and we will have a plot, but no one has it now.

DR. RODEN: I understand.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: Well, just to take Dan's point one step further. It does seem, in this drug, that there is a disparity in the time course of the pharmacokinetics and pharmacodynamics. In fact, raising, you know, pointing in the opposite direction from what Dan is saying, that is to say that even if we see disappearance of the bolus effect on concentrations early on, we don't know to what extent

that is influencing wedge pressure several hours later in this drug.

DR. ALLGREN: Well, except that the slides that I showed, the slide that I showed comparing the results at one and a half hours in study 306 and 325, that was looking at the actual effects on wedge one and a half hours after the initiation of drug.

And there is really no difference on the level of the effect on wedge at that time. So that would suggest that the use or non-use of the loading bolus was really not making a difference in the pharmacodynamic curve.

DR. LIPICKY: Right. If the infusion is over the top of the dose response.

DR. ALLGREN: Pardon me?

DR. LIPICKY: Nothing.

CHAIRMAN PACKER: Any other issues related to hemodynamics or pharmacodynamics before we go on to symptoms?

DR. GRINES: I just have a quick question about the slide where we are comparing the hemodynamic effects with and without bolus. And I wondered how

many patients we have measurements on with and without bolus.

DR. ALLGREN: In that particular study, study 306 had about 8 patients per group, and study 325 had about 42 patients in the group.

CHAIRMAN PACKER: Can we go on to symptoms? And I think the study we are really focusing on is 325. I'm sorry?

DR. SAMBELL: I'm Dr. Nancy Sambell, and I do have some plasma concentrations, if you want to take down some numbers. I did the pharmacokinetic analysis on all of the studies, so I can generally speak to the characteristics.

CHAIRMAN PACKER: Can you just speak a little bit louder, please?

DR. SAMBELL: Do you want the numbers, or do you want me to just generally characterize what the plasma concentrations were?

I have the first level at 15 minutes, and the control is around 750, and the .015 group is approximately 2,000; .03 is approximately 3,800; and at three hours the level for the first group is about

3,000, and for the second group about 3,700.

Do you want 24 hours? 24 hours about 2,800 for .015, and 3,400 for .03.

CHAIRMAN PACKER: And the levels on placebo?

DR. SAMBELL: And for placebo at -- you have 15 minutes, at three hours 830, and 24 hours about 600.

And I should point out that this includes, even though they were randomized to these different groups, the levels do reflect what you might have -- includes the dose reduction. So this isn't a pure concentration dose correlation.

You have to take into account that some people did reduce their dose. But, basically, the concentrations are reached quite rapidly within the steady state concentrations that you would see are reached quite rapidly with the bolus.

But you do see somewhat of a lag between the concentration and effect, and that is why that bolus isn't really contributing appreciably to the overall effect with the infusion.

I think we are on a graded dose response curve. Some analyses we have done with concentration effect suggests we are in the graded part of the dose response curve. And simply this lag characteristic that is not making that smaller bolus dose contribute appreciably.

DR. RODEN: I understand what you are saying. So these are concentrations with a bolus, without a bolus, since the half life was 20 minutes, without a bolus you would expect steady state in about 100 minutes, or one and a half hours.

So if there are pharmacologic effects that occur that we observed in this study, within 30 to 60 minutes, those have to be attributable to the bolus.

I mean, I think that is a fair thing to say. And it seems to me the cardia index effects that you are seeing are very, very early. So they must be bolus effects.

I mean, that is -- I think we ought to probably leave the discussion of the doses until we have the safety discussion as well, because --

DR. SAMBELL: I think your terminal half

life is about 15 minutes, and you are at 90 percent of your steady state at three half life. So you are talking about less than an hour to reach near steady state concentrations.

DR. RODEN: Well, the FDA document says 20 minutes, and you can split hairs about when you are at 90 percent.

DR. ABRAHAM: And I will just add, having done of the two only studies without a bolus, a loading bolus, that is protocol 306, which was simply a four hour continuous infusion, that we measured significant changes in pulmonary capillary wedge pressure occurring within 30 minutes of the start of the infusion.

And, in fact, the curve we did very frequent measurements of hemodynamics early in the course of that study, the curve begins to drop within 15 minutes. The 15 minute time point is already done without a loading bolus.

CHAIRMAN PACKER: Can we move on to symptoms? Comments on symptoms, any follow-up on Marv's original questions on symptoms?

Dan?

DR. RODEN: I have, I think, a quick question. There is this -- now I have to find it. The graph that shows the changes in the four symptoms together, the appetite, dyspnea, the fatigue, light headedness.

DR. ALLGREN: Slide 24?

DR. RODEN: Yes. I guess my question is, maybe I'm just not enough of a heart failure doctor. I'm not sure I would have thought to ask somebody whether their appetite is good or bad after a six hour bolus of something, or 6 hour infusion of something, sorry.

And so my question is, how many different symptoms were asked about, in fact? We see four here. Is this --

DR. ALLGREN: These were the four.

DR. RODEN: So in the protocol there is a statement that says we were going to ask about dyspnea, we are going to ask about fatigue. Ray is nodding his head. So this is not just a selection that you sort of --

DR. ALLGREN: Right.

DR. RODEN: -- smorgasbord you are showing us. Okay.

CHAIRMAN PACKER: Can I just clarify this? Maybe you can -- the FDA reviewer, I think, picks up on what Dan just mentioned. And just so that we understand exactly what happened, at six hours in protocol 325, what actually happened?

And please describe the -- what measurements were taken, when they were taken, what the investigator or coordinator was then supposed to do in terms of unblinding, and what happened when, and who -- and I know this is going to sound like Watergate, but who knew what when?

DR. RODEN: Your political analogy is a little dated.

CHAIRMAN PACKER: It depends on what is, is.

DR. ALLGREN: At the end of the six hour period they were supposed to measure, still blinded, they were supposed to measure the six hour pulmonary capillary wedge pressure measurement, and the rest of

hemodynamics.

They were also, the patients global clinical status was supposed to be assessed by one of the study staff asking the subject how they were feeling, and the physician also completing a rating of how they thought the subject was doing.

The subject and physician, together, were supposed to rate these four symptoms. Again, just being asked how their breathing was, and rating it as either worse, no change, or improved from baseline.

At that point the investigator called a central -- the computerized randomization system, which was being maintained by a separate unit, the Maryland Medical Research Institute.

They would call there, enter the patient number and information, enter the fact that the six hour assessments had been done, enter the six hour wedge measurement, and at that point the computer would unblind them, and tell them whether the patient was on Natrecor or placebo.

The two doses of Natrecor remained double blinded, even after that fact, but they were told

which of those two that they were on.

CHAIRMAN PACKER: So according to what you said the sequence was that they made all the assessments they were supposed to make at six hours, they called up the unblinding number or system, and confirmed that the measurements had been made, transmitted the primary endpoint, which was pulmonary wedge pressure, and then got the code, not according to dose, but --

DR. ALLGREN: Right.

CHAIRMAN PACKER: -- but just placebo or active therapy?

DR. ALLGREN: Right.

CHAIRMAN PACKER: That means that they -- that what you were able to confirm before the unblinding specifically was the primary endpoint of wedge pressure, but not of any of the other secondary endpoints.

In other words, the endpoint, the wedge pressure, which is the primary endpoint of the study, was recorded in the telephone?

DR. ALLGREN: Right, but not --

CHAIRMAN PACKER: But the other endpoints, which should have been made before unblinding were not transmitted before the code --

DR. ALLGREN: Right.

CHAIRMAN PACKER: -- was broken. And how do you know?

DR. ALLGREN: They would have been recorded at the site. The sites kept source documents which would be sort of a worksheet that would have these rating scores. That was the site source document for these assessments, and that is what we would monitor against when we were monitoring sites.

CHAIRMAN PACKER: And I think you said that you did find discrepancies in looking at that when you went out and monitored the sites.

And I guess the additional difficulties in knowing how to interpret the times, is that the clock that is on the wall, or the watch that someone is wearing, and the clock in the analysis center, unblinding center, may or may not be recording the same time.

And this makes it really difficult. I

guess -- let me ask a question. There was an amendment to the protocol that specified that instructed investigators exactly how to do this.

DR. ALLGREN: That was done very early in the study at about maybe 15 patients being enrolled, and no data had come in house at that point.

CHAIRMAN PACKER: When did the trial -- forgive me, when did the trial actually start recruiting patients?

DR. ALLGREN: Date wise?

CHAIRMAN PACKER: Yes.

DR. ALLGREN: I have to look that up.

CHAIRMAN PACKER: I will tell you why I'm asking. The only information that we have from the FDA reviewer is that the protocol was finalized in June.

DR. ALLGREN: Yes, that is --

CHAIRMAN PACKER: The amendment was submitted in December, and the protocol ended recruitment in April.

DR. ALLGREN: Yes, that sounds right.

CHAIRMAN PACKER: So the -- but when did

recruitment begin?

DR. ALLGREN: In that fall, the first few month's enrollment was very slow, and then enrollment picked up after the first of the year.

CHAIRMAN PACKER: Okay. Can I just ask a question that Marv -- how do you think that the knowledge of the hemodynamics might have influenced the assessment of symptoms?

DR. ALLGREN: I really can't address that directly. The study staff would have had access to the hemodynamics as we had discussed. But I think it is worth noting, as I mentioned, that in study 326 similar results were obtained, and there, there was not Swan-Ganz monitoring in the majority of patients.

CHAIRMAN PACKER: 326 is really hard to interpret, because it is active controlled, and showed no difference.

DR. ALLGREN: Right. But, again, about 60 percent of the patients were reporting improvement at that six hour time point. And that study was being done in parallel with study 325. So nobody would have known the results of the other study while it was

going on.

CHAIRMAN PACKER: 326 is still very -- I would like to focus on 325, because it is your placebo controlled trial, on symptoms, and it is the one that shows a difference as opposed to a similarity, or the lack of a difference.

The -- because I think that there is a tendency, I think, that we all have in monitoring patients in the CCU is to believe in hemodynamics. We all -- we are not only trained that way, we actually I think believe it.

We think that if the wedge pressure goes down and the cardiac output goes up, we must be doing some good to patients, otherwise we wouldn't be doing these things and monitoring these things.

And I think I'm concerned that it would be so easy for me, watching the wedge pressure go down, to conclude that the patient was better, even if the patient wasn't better, and that would be doubly true if I actually told the patient that the wedge pressure was falling, which we frequently do.

And then the patient gets the impression

that they are "responding", we get the impression that they are responding. And it is really hard to not conclude that there is some improvement, and that improvement would be easily transmitted in any scales one wants, in terms of recording that improvement, symptomatically, or clinically, had occurred.

The reason for being concerned is that I can easily appreciate if I've made a few assumptions, how a drop in wedge pressure could result in alleviation of dyspnea, and I could easily appreciate how perhaps an increase in cardiac output could reduce fatigue, although that I'm less certain about.

But you found a very close correlation between dyspnea and changes in wedge pressure, which is either suggestive that they are physiologically related, or pathophysiological related, or that the bias that we are concerned about actually occurred.

What I'm concerned about is why would a drug that lowers wedge pressure or increases cardiac output, and decreases wedge pressure, and decreases blood pressure, improve light headedness? Especially given the fact that this drug produces more

hypotension than placebo.

Why would a drug improve appetite in six hours, when this is a drug that is associated with nausea in the side effect profile?

DR. ALLGREN: Well, the adverse events you are referring to, which will be discussed in more depth are occurring in a small number of patients.

CHAIRMAN PACKER: Why would a drug -- there was also another measurement done in this study which was edema. Edema was also significantly reduced with this drug in six hours, even though there was no reason that edema should be reduced.

Consequently I'm getting the distinct impression that there was an investigator or a coordinator that knew the wedge pressure was falling, and said the patient must be better, and began to check, improved, improved, improved, improved, improved, across a whole variety of scales and measures, including scales and measures that couldn't reasonably be expected to improve, and in fact could reasonably be expected to be adversely affected, specially light-headedness.

DR. ALLGREN: I don't -- you raise some good points, but I think there are a number of things here. I mean, first of all, there was a differential response with a number of these symptoms. Dyspnea and fatigue was something that a majority of patients reported a response to, whereas the light-headedness and appetite a smaller number of patients were reporting an improvement in.

I think it is possible that a drug like Natrecor could be improving both of those things. With regard to appetite, some of the decreased appetite in these patients that could be due to either congestion or it could be interrelated with the dyspnea, and improvement in that could lead to improvement in those symptoms as well.

But with regard to your last point, if I could have backup slide 202, this is looking at the issue of if an improvement was reported in one symptom, was there automatically an improvement reported in other symptoms across the board.

And what you are looking at here is, on the -- across this side is the response at six hours

on change in fatigue, and the change in dyspnea across here.

And so, for example, you can see that there were 19 patients who reported no change in fatigue, but had an improvement in dyspnea. And you can read the other blocks around.

So it was not the case that a patient would automatically report an improvement in all symptoms across the board.

CHAIRMAN PACKER: I guess I'm more concerned, looking at this, than reassured. But more of my concern is raised by the fact that -- I guess I don't understand how this drug would improve light-headedness.

DR. ALLGREN: Dr. Horton, did you want to address that?

DR. HORTON: Yes, if Dr. Packer would acknowledge me. I'm Darlene Horton from Scios, thank you.

If I could have the core slide number 24, this might help clarify some points. I was actually the person that came up with this symptom scoring

system, which was not an easy feat, as you can imagine, having talked to a variety of heart failure colleagues and advisors, and was actually fairly discouraged from doing this in the first place, because there was a very strong belief that we wouldn't show anything within six hours.

For one thing we decided to include light-headedness and appetite because we really did not expect for those things to be improved, whereas we did expect for dyspnea to be probably the most likely thing that would improve over six hours.

You pointed out that there may be some bias on the part of the investigators and subjects because of their knowledge of the hemodynamics. And, in fact, when you look at light-headedness and appetite, the .03 group, which has much more significant hemodynamic effects, has fewer patients that report an improvement in these symptoms.

So I think we are seeing a little bit of just background noise, subjectivity, and I think there is also -- this also demonstrates a situation where there is a real difference between statistical

significance, and clinical significance.

For example, I'm not sure we would think that it is really all that meaningful that fewer than 25 percent or 30 percent, 27 percent of patients had appetite improved, but yet it is statistically significant in one of the dose groups.

Still the more --

CHAIRMAN PACKER: The only, the concern -- the concern is that if someone is getting the impression, by looking at hemodynamics that a patient is a responder, however one gets that impression, by looking at wedge pressure or cardiac output, or whatever, and one then trans -- and that creates an impression in the person's mind as they go -- as they both interact with the patient, and interact with the case report form, that the bias is unavoidable.

I don't know, you can't -- I don't know how it could be avoided. And I think you are quite right, in some ways, light-headedness and the appetite here was your positive control, you didn't expect there to be any change.

And, you know, I think that it is correct

that those involved in research in heart failure wouldn't expect anything here, and in fact would have said, don't measure it because you are not going to see anything.

The fact that you did see something, it doesn't matter that it is big or small, or whatever, but that it is not that much smaller than some of the other measurement, it just indicates that at least some investigators, maybe more than just some were just saying, responder, responder, responder.

And edema doesn't -- it doesn't change in six hours. You didn't get a big diuretic effect of this drug. It is just impossible.

DR. HORTON: Yet, as you are pointing out, the most extreme comparison would really be to look at the placebo group and the .03 Natrecor group, and if you just look at those two groups there is really no appreciable difference between them.

CHAIRMAN PACKER: Jay, actually you were first.

DR. COHN: I hate to belabor this point, because I think we are all aware of the limited value

of this kind of an assessment. There is no question, and I think we all are comfortable with the fact that if the pulmonary wedge pressure falls patients do feel better. And maybe it is a bias that we've all grown up with, but the observations at the bedside, for years, have confirmed that, that that happens.

And what I'm surprised about, in trying to asses these symptoms scores is that this was done, really, as an interaction between the investigator and the patient, apparently, and a case report form was filled out.

It would have been far better had this been done in some sort of a blinded way by the patient himself, or herself, using some sort of a linear scale, or something, to mark down how they were feeling, in which there was no interaction with the investigator.

And, of course, it would have been very important, in the protocol, to make it clear that the investigator was not to convey to the patient any information about what had happened to the pulmonary capillary wedge pressure.

But since that wasn't apparently part of the protocol, and this was done as an interaction, I think there is no way to turn this kind of data into a comfort level that all of us would say is an objective assessment of system relief. It is nice that it went in the right direction, and at that point I think we probably have to trash it, because we recognize the weakness of this kind of analysis.

CHAIRMAN PACKER: And I guess one thing we -- just based on what we were saying before, one would add is that after the patient would fill out the form, independent, without any knowledge of the hemodynamics, etcetera, that the information on that form should be transmitted to a central data place before the code was broken.

DR. COHN: Or the code was broken.

CHAIRMAN PACKER: Bill?

DR. ABRAHAM: You know this is imperfect, and I'm troubled by the data, as well. But while I do agree with your focus on protocol 325, since it is a placebo controlled study, I'm reassured a bit by the findings in 326 because of the concordance between the

two studies in regard to symptom assessment.

And, in fact, rather than being put off by the active control, I think I'm heartened by the active control, because as many patients got better in the active control group, which was mostly inotropes, as they did in the Natrecor group, as I would expect to happen. I don't think I would expect Natrecor to be it.

CHAIRMAN PACKER: It is just that I guess the history of this can be processed as found that active control trials that show no difference are very hard to interpret.

DR. KONSTAM: I just want to say a couple of things. One is just in terms of 30,000 foot view on this. I mean, I agree with what Jay said. I think that we are forging new ground here in trying to ask studies looking at hemodynamic effects to show effects on symptoms.

This is sort of a first shot at it, and in fact it was designed before the new guidelines were developed, and I think that we have to put all of that in perspective.

And what I'm going to be looking for here -- maybe that is different from others, is just confirmation in the symptoms that the wedge pressure is probably meaningful, rather than looking to the symptoms as the definitive thing. So that is my general point.

My specific point, I just want -- could we get that slide back up again, because I actually think that --

DR. ALLGREN: Which slide are you --

DR. KONSTAM: The last slide that was just shown.

You know, I do get some information here, and I think that I'm glad that you put this up. And so I think we are all going to agree that there is a problem, there is a significant problem in this analysis.

But we do get a little bit of handle on it here, I think. One, because I think these two right-hand measurements, the .015 bars, the yellow bars on the right-hand side I think give you an idea, perhaps of the amount of noise going on.

And I also think, though, that this study, as opposed to 311, there was dose response with regard to pulmonary capillary wedge pressure, whereas if you look at these two bars you don't see that, which gives me some degree of assurance that, you know, that this noise that we are seeing is not heavily being driven by bias, based on the wedge pressure, to some extent.

It is not perfect, but I guess I think this is probably the best we are going to do with this.

CHAIRMAN PACKER: I think it is the best we can do. And maybe we need to make a few points. First of all, this represents the first symptom data in acute heart failure this committee has ever seen.

It is the first attempt, by anybody, to show that IV drug for heart failure does something other than improve hemodynamics. And this Committee would be remiss at not, one, making note of that. Two, saying that this is a really good thing to do, and we are really glad that the sponsor did it, and that it is much better to have done this than to have

relied on just looking at hemodynamics as the sole source of support for a claim.

As is not uncommon when one does things for the first time, one learns about the kinds of things that can occur in measuring these things. So many of those have been brought up today, and there is probably further refinements that will be made in the future.

And I think it is important for us to make note of the concerns in how one approaches this, not only for today's discussion about this NDA, but for future discussions about future drug development programs, because this is really part of the process for today.

And that I think that we can all take a look at this and reach our own judgements as to whether there was bias, and how much bias. And I think it is impossible to say.

Marv, I understand that you might want to take what is on the right and subtract it from what is on the left and say -- I'm not saying you are doing that, but basically say that that is your noise, on

the right, and therefore if one subtracts it from the left, that one would be able to get a sense of how many investigators just checked things randomly based on knowledge of a wedge pressure.

Maybe one can do that, maybe one can't do that. But I think that this is the first attempt to move forward on this. You know, I'm not certain that we can expect that the first attempt is going to be perfect, and it is important to highlight what the imperfections are so they will not be reproduced in further NDAs.

Cindy?

DR. GRINES: I just would like to make a comment that I'm impressed by the fact that we have assessment of symptoms based on intention to treat. And I would like to contrast that with yesterday's application, where this was never shown to us, and what was shown to us is afib versus patients who reverted back, or were normal sinus rhythm.

I mean, the patients were probably aware of that, we never saw an analysis of intention to treat, and yet everybody on the panel seemed to be

pretty convinced that maintenance of normal sinus rhythm was a good thing.

So I think that now we are talking about assessing this particular product more strictly. And maybe the panel should come up with an agreement on a way to asses symptoms.

CHAIRMAN PACKER: Well, we are not going to do that right now.

DR. PIÑA: As a continuing comment on the assessment, the fatigue assessment is made with moderate activity, and with minimal activity. And if these patients were at bed rest with a Swan-Ganz catheter on, how can that be assessed?

DR. ALLGREN: At the various follow-up time points they were just simply asked about these symptoms and whether, with regard to them, they felt that they were worse, no change, or improved from pre-treatment.

CHAIRMAN PACKER: I must say, Ileana, I hadn't actually thought about that. There was a baseline assessment of dyspnea in this trial, and these patients were dyspnea at rest?

DR. PIÑA: Some of them were.

CHAIRMAN PACKER: How many were dyspnea at rest?

DR. PIÑA: There were ten in the placebo group, 13 in the low dose group, and 13 in the high dose group at rest.

CHAIRMAN PACKER: So I guess, Ileana, you are -- I think you are asking, how does someone who doesn't have dyspnea at rest get better?

How does someone at dyspnea at rest -- who doesn't have dyspnea at rest get better?

DR. ALLGREN: They can have it an improvement in just how their breathing is feeling compared to pre-treatment. I mean, that was just the basic question that they were asked.

We did do --

DR. COHN: They didn't know they were dyspneic until they got better.

CHAIRMAN PACKER: Okay, I think. Ray?

DR. LIPICKY: That is okay, I think.

CHAIRMAN PACKER: But I think we have to think about it more.

DR. LIPICKY: Yes, but I mean, you may not be huffing and puffing, and therefore not qualify as being dyspneic, but in fact you breathe easier when your lungs aren't as stiff, and you would say I'm breathing better.

I mean, it is just a semantic thing.

CHAIRMAN PACKER: I know. Maybe we will -- does anyone else have any comments on symptoms?

DR. GRINES: I would just like to point out that also we see a lot of heart disease at our institution, the very same thing happens. The patients don't realize they are symptomatic until you've done something to correct it.

CHAIRMAN PACKER: Marv? I think we are going to be through, except for the fact that it sounds like there is a sense, at least around the table, that the concept of looking at symptoms here is something that people liked about looking at these data, whether they are terribly flawed, or moderately flawed, or whatever.

I guess that means that the era of surrogacy in acute IV heart failure has come to a

close.

DR. GRABOYS: I'm not sure we have to obsess too much longer about this. And I'm sitting here, thinking to myself, as a doctor who takes care of folks who have heart failure and a lot of other things, is this drug going to help, and are they going to feel better?

And the patient could come in in pulmonary edema and I give him morphine, they are still in pulmonary edema but they feel great. So, you know, from my point of view, at this point in time, and I can't obviously speak for the safety issues, the sponsor has presented information which is helpful to me because I see that there is significant hemodynamic improvement.

And, yes, this is flawed in terms of subjectivity as far as -- but the fact is that they do feel better, and the hemodynamics underscore that.

So that is where we are at this point in time, and I think we should move along.

CHAIRMAN PACKER: All right.

DR. LIPICKY: Maybe it is worth a minute

longer, right? I mean, this idea that you get the approval of a new treatment because you can demonstrate that you make people feel better, or live longer, or both, I think is a pretty fundamental notion.

And if wedge pressure is the only thing you are looking at, you indeed are looking at a surrogate. And the difference between today and yesterday was that some people really thought you had to make people feel better, because sinus rhythm wasn't the important criterion.

So the Committee is sort of going through its shift in bias here, with respect to whether sinus rhythm is the big deal, or wedge pressure is the big deal. And we, as an Agency, would like to see, in fact, both things measured.

And so the thing that is being gone through here is to not be satisfied with wedge pressure, to in fact document if people really do get better when their wedge pressure goes down, you ought to be able to document that pretty easily. They made a pretty good attempt, and you took them over the

coals.

And so it is harder than you think. And although the doctors at the table all think that wedge pressure says you feel better, no one has ever been able to show that. There is no set of objective data that passed scrutiny that confirmed what everybody knows, so maybe it is not true.

CHAIRMAN PACKER: This is a focus of the last question of the day, and I don't want to necessarily spend any more time on it.

But, Marv, you said you had a question other than symptoms?

DR. KONSTAM: No, I just wanted -- until you made your last statement I just -- I don't agree with it. So, you know, I mean I think we are having a lot of problems with the symptom data set here, and there are a couple of different reasons for it.

We have focused, in the last few minutes, about how we make those measurements, and what they mean, and how we maintain blind and all that stuff. Some of those are correctable, I think some of those are not going to be correctable.

Furthermore this reflects back to the population question, because you can't improve dyspnea at rest if you are not dyspneic at rest, which means maybe this is not exactly the right population, but then again maybe you can't study the right population in a randomized control format, at least we've never seen a study like that.

So for all of those reasons, you know, I'm not at the point personally of saying, I would like to move away from hemodynamics as primary endpoints in these studies.

I guess we can talking about it later, but I'm --

CHAIRMAN PACKER: I'm sorry, let me clarify at least what I had put forward as a hypotheses, which was not that hemodynamics should or shouldn't be the primary endpoint, but that what this committee would like to see is a valuation of clinical status, or some meaningful clinical outcome in addition to hemodynamics.

And I think Tom has emphasized that, as well. Not that that has to be the primary endpoint,

but that the absence of any such data would be considered to be an important omission in a data base.

And I think that that is an appropriate summary of where we are, and that is a change from the past. That is a change from the past.

Now, whether how to asses those symptoms, which symptoms to asses, what the problems are, which patient population; the nice thing about it is that each drug presents its own challenges in that regard. Some of them are general, some of them are drug specific, and they may or may not be perfect solutions, but what we are doing is welcoming the data to help us clarify that.

Jay?

DR. COHN: The only point I would make is that I would hate to leave the impression that a six hour symptom score should now become the standard for assessment of a hemodynamic effect of a drug.

I think we would all feel more comfortable if there were some objective assessment at a somewhat later time frame, so that there would be time for things to get better, such as appetite and fatigue.

CHAIRMAN PACKER: Jay, let me ask a question. We actually had -- that is one of the questions to the Committee, and I just wanted to get a sense from the Committee, since you just brought it up, no one has actually given the concerns about unblinding, concerns about interaction of knowledge of hemodynamics and recording of symptoms, we haven't actually talked about when these symptoms were actually assessed. They were assessed at six hours.

Which in the trial that that was occurred, that that was appropriate, that was the end of double blind therapy. But not too many of these patients are going to get an infusion for only six hours.

And much of the clinical relevance of what occurs, occurs beyond six hours. How comfortable is everyone, is the short time frame here for the symptom assessment yet another concern that should be added to the list of symptom assessments?

I think, Jay, you are saying yes, people should rethink when they are going to evaluate symptoms. Is that the case?

DR. COHN: Well, I think it will depend

upon the intervention. And I think the trouble we are going to have here, and this is still to come, I guess, is how to translate this clear hemodynamic effect, despite all the arcane issues about exclusions and intent to treat, I think that there is no question that this drug has a vasodilator effect and produces hemodynamic changes.

And we are all comforted by the fact that people didn't have terrible headaches, or nausea, or vomiting. I mean, we are more concerned about the adverse effects on symptoms than we are -- that lowering a wedge pressure makes a patient feel better.

I think that is easy to understand, but if you do it with a drug which causes diarrhea and vomiting, it would not be a very favorable quality of life improvement.

So I guess to the extent that we have six hour data showing that the infusion didn't have adverse effects, an the symptom relief sort of tracked with the hemodynamic effect comforts us.

But now the question being, how does one translate this data in these trials into the clinical

application of this therapy, and what sort of endpoint should we be seeking for clinical management, becomes a far more difficult issue.

CHAIRMAN PACKER: Any other issues? Marv, you had one other?

DR. KONSTAM: I just want to bring up another issue before we go on to the safety presentations.

CHAIRMAN PACKER: Yes, please.

DR. KONSTAM: At some point I would like to see some of the data summarizing urine output and Is and Os. I don't know whether you are planning to show that later, or whether we should look at that now?

DR. ALLGREN: We could look at that in --

CHAIRMAN PACKER: Is that part of safety?

DR. ALLGREN: No. Slide 203. This is looking at the mean urine output in patients enrolled in study 325 during this initial six hour period. And as you can see there was a dose related increase in urine output accompanying Natrecor administration during this period.

Now, would we -- we didn't continue to follow detailed Is and Os throughout the hospitalization, but we did follow serial weights. And if we see slide 204, this is looking at weight loss in these patients over the first five days of hospitalization.

And if you look at day 2 you can see that there was, in essence -- remember, now, these patients are getting -- it is labeled placebo, but they are getting placebo for the first six hours and after that they are getting standard care agents, so that is slightly mislabeled.

But, anyway, on day two there was, in essence, no net weight loss in the control group, whereas there is in the two Natrecor dose groups, and you can continue to follow the patients over time and see progressive weight loss, presumably due to diuresis in these patients over the first five days.

DR. KONSTAM: Well, thank you. I just want to comment that I'm looking at all of the data, and all of the studies. I'm confused about exactly what this drug does to urine output and total volume

status.

I'm surprised that I don't see, in fact, looking at all the data set, a clear naturietic effect, and I just wondered if you could help us a little more with that, with summarizing -- I mean, you've selected a couple of endpoints at one or two time points in one study.

But I wonder -- well, I guess I would like to ask you the question what you think this drug does, and maybe support it or not with the entire, you know, with a summary of the entire data on this subject..

DR. ALLGREN: In preclinical studies, and in studies in normal volunteers, Natrecor has been quite consistently associated with a diuretic and a naturietic effect. I think the results on this end study in patients with CHF has been more variable.

And one has to keep in mind that there is somewhat of a confounding effect, given that these patients are routinely on diuretics, and the doses of these diuretics can be changing.

If we look at our CHF studies with Natrecor in study 307, we did see an increase in

diuresis and naturiesis on the -- in the patients, the days they were receiving Natrecor as opposed to the cross over days when they were receiving placebo.

That difference might not have been statistically significant, but there was a trend of an increase in diuresis and naturiesis with Natrecor administration in that study.

And that was a study in which diuretics were being held during the dosing period. If you look at study 311, in that study we did not see an increase in diuresis and naturiesis in the Natrecor patients compared to placebo. As a matter of fact, actually, urine output over the 24 hour period was a little less.

If I could have slide 145? This is looking at diuretic usage in that study, and the top line is looking at the percent of patients who receive diuretics in the 24 hours preceding drug dosing, and the bottom line is diuretics during drug infusion.

It is interesting to note that if you look at the placebo patients, in the 24 hours prior to beginning study drug, 45 percent of the placebo

patients were reported to have gotten a diuretic, whereas the patients being randomized into the Natrecor groups had been receiving higher doses of diuretics.

Now you look during drug infusion and you see the percent of placebo patients getting a diuretic is increasing, whereas the percent of Natrecor patients getting diuretics is decreasing.

And, as you remember, in the study it didn't show a net change in urine output, but there is a differential use of diuretics going on here, which would be consistent with the drug having some underlying diuretic effect.

Then I showed you the results from study 325 during the initial six hour period where diuretics were being withheld. We, again, did see a dose related increase in diuresis with Natrecor.

Where, say, if we look over the entire first 24 hour period we did not. But, again, there was differential diuretic use in that study, as well. I can't remember if I showed you that slide.

DR. MOYE: Excuse me, just one second.

Those are very small numbers to draw such sweeping conclusions from. I mean, you have ends of less than 30, in some cases less than 25. And for what they are worth, the P values here are kind of high.

So I don't know that we can be too confident.

DR. ALLGREN: Well, it is just looking at a general trend. And if I could have --

DR. MOYE: But general trends aren't very helpful sometimes. You know general trends can be as much random sampling variability if anything else. That is my only point.

CHAIRMAN PACKER: Also I think before we spend too much time on that, I think it is entirely natural within the usual clinical setting, that if the wedge pressure is lower, that the use of diuretics will be less than when the wedge pressure is higher, and the wedge pressure was lower in the patients getting active therapy than the patients on placebo.

So I don't think anything here is particularly surprising, and it is pretty consistent with the way people would practice medicine.

Jay?

DR. COHN: Following up on Marv's sense of confusion here, I'm confused as well, as to whether you are claiming that this drug is a naturietic agent or not. The name of the drug suggests that it is naturietic, and that is a little disturbing.

You have a cartoon, though, that does include diuresis/naturiesis as one of the actions of the drug. The data really don't support it, and I guess the interaction with other diuretics raises the issue as to whether your thought is that this drug is diuretic by itself, or whether it in some way interacts with a loop diuretic to augment the loop diuretic effect, or whether it has no discernible effect on urine output.

It seems to me that that has to be resolved in labeling of this drug, as to whether physicians should or should not be led to believe that this drug will produce diuresis.

So what is your position at this point? This data are certainly not very persuasive on the naturietic effect.

DR. ALLGREN: Well, as I mentioned I think the drug does have a diuretic and naturietic effect in the pharmacological sense. I mean, in normal volunteers. In the patients with CHF I think that the drug demonstrates a diuretic effect if it is being studied in a setting in which diuretic usage is either being held or maintained constant.

But that is confounded by the differential diuretic usage in the studies.

If I can have backup slide 215? I mean, this just finishes that thought in that the beneficial effects of Natrecor are being achieved, in general, with less diuretic usage across the board in our studies.

This is looking at -- the top line, diuretic usage during the first 24 hours in study 325, and the bottom line is diuretic usage at any time during the pre-ental vasoactive treatment period in study 326.

And in both you see this trend for decreased diuretic usage while these patients are showing an improvement in clinical status.

CHAIRMAN PACKER: Dr. Roden would like to see changes in urinary sodium, which he would remind us, is what defines naturiesis.

DR. ALLGREN: I don't have a slide of that.

DR. ABRAHAM: I could actually share some data from protocol 306 if you would like, and I --

DR. GROSSBAR: We are not making a claim that the drug is clinically a diuretic. The data are confusing, they are certainly not overwhelming, they can't replace the use of ordinary diuretics in the management of heart failure.

We have followed this over several studies, sometimes there is some effect, sometimes there is less of an effect.

Most people who treat heart failure would not think it was a substantial effect, and so we've observed it, reported it, but we do not claim that this is a diuretic.

DR. COHN: Are you at all uncomfortable with the name of the drug, Elliott?

DR. GROSSBAR: We didn't name it. It is

B-type naturietic peptide, it is not our name. We got rid of the brain, that is a step forward.

DR. ABRAHAM: Well, I think in large part Elliott took the words out of my mouth, but I do think what the drug may suffer most from in the long term is its name. This class, in general, the naturietic peptides, and as many of you know the effects of naturietic peptides on the kidney has been a major focus of my own research.

And, basically, what we've shown is the response is very heterogenous. This is why the data looks as it does. In fact there are responders, and there are non-responders.

And what we have been able to best correlate with the renal response to naturietic peptide is distal tubular sodium delivery. That is, if you are not delivering sodium to the site of action of a naturietic peptide, you don't get naturiesis. And if you deliver it there you do.

And it is a highly variable response among heart failure patients. But I would agree with the company's position, this should not be marketed as a

naturietic or diuretic agent.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: You just made a statement that confused me. You said diuretic use was stable, not changed. I thought during the first six hours of 325 there were no diuretics administered?

DR. ALLGREN: Right, right, right.

DR. PIÑA: Do you have any thoughts as to whether the improvement that you see here, in urine output during the first six hours could be related to an improvement in cardiac index as opposed to a variable effect on the kidney?

DR. ALLGREN: That is possible. We just measured the urine output during that period, we didn't directly asses the mechanism of it.

CHAIRMAN PACKER: Does anyone have any other questions about efficacy? One brief question. There was a change in either formulation or synthesis of the drug to a recombinant form. Is that correct?

DR. ALLGREN: Pardon me?

CHAIRMAN PACKER: Is that correct?

DR. ALLGREN: Yes, the early studies ere

done with drug made by synthetic methodology, and the later studies, and the commercial product will be a drug made by recombinant DNA the company. Both have the identical amino acid sequence to the endogenous BNP molecule.

CHAIRMAN PACKER: And the FDA reviewer made note of the fact that about 50 percent of the patients in the clinical trials got the first type, and fifty percent -- this is approximately -- got the second type.

Is the FDA, are the FDA reviewers comfortable that the difference between these two is not an issue to the committee?

DR. LIPICKY: Yes.

CHAIRMAN PACKER: Good. Let us take a ten minute break.

(Whereupon, the above-entitled matter went off the record at 11:30 a.m. and went back on the record at 11:42 a.m.)

CHAIRMAN PACKER: If we can have everyone take their seats, and we will proceed to the safety presentation.

DR. HORTON: Thank you, Dr. Packer. Good afternoon.

In this safety summary today I will show you that the safety data from the Natrecor NDA support the use of Natrecor for short term treatment of congestive heart failure.

I will first review the clinical characteristics of the patients enrolled in the studies to show you that they well represent the target population for which Natrecor would be used.

I will then show you that there is no evidence for an increase in mortality with Natrecor use, then I will generally review the adverse event profile to show that Natrecor generally was well tolerated, and that the adverse event profile is very well characterized.

Finally I will show you data about outcomes after discontinuation of Natrecor to show that there is no evidence for an increase in the need for hospital readmission.

Let me begin by reviewing the safety data base.

A total of 787 patients have received Nesiritide in clinical studies. These come from pharmacology studies in the literature, from a small study of Natrecor for another indication, and from the 505 patients who received Natrecor in the Natrecor CHF program.

Of these 505 patients who received Natrecor in the NDA for CHF 111 of them received Natrecor as either a single IV bolus, or multiple IV boluses for less than 24 hours.

Of patients who received Natrecor as a continuous infusion, which is the recommended dosing regimen for Natrecor, the majority of those patients received Natrecor for more than 24 hours, with the bulk of them receiving Natrecor for 24 to 72 hours.

Many patients also received Natrecor for more than 72 hours, and the longest duration to date is 9 days.

To review the demographics, a total of 721 patients were enrolled in the clinical studies, in eight clinical studies. The mean age was approximately 60 years, and about a third of the

patients were more than 65 years of age. Women represented approximately 30 percent of the data base.

All patients in the Natrecor CHF program had chronic congestive heart failure. And as you can see here, most of them had neo heart association class III and IV.

In the two larger studies, study 325 and 326, which Dr. Allgren already described to you, we also collected information about the patient's baseline medical and cardiac histories. These were typical CHF patients with a variety of co-morbidities, as you can see here, with a high percentage of patients having a history of hypotension prior to entry into the study, a history of a previous myocardial infarction, diabetes, and about 30 percent, or about a third, had chronic renal insufficiency.

It is important to note that a history of arrhythmias also did not exclude patients from participation in the studies. And, again, you can see that many of these patients had arrhythmias such as atrial fibrillation, frequent PVCs, and ventricular tachycardia.

I'd like to also add to put a little more perspective to the patients that were enrolled in the 325 study, that another indication of the level of decompensation for these patients is, for example, their baseline norepinephrine levels, which in study 325 was a mean of 700 with normal being below 300. And the range of these values ranged from 200 to 1,800.

In addition we had, of course, baseline BNP levels themselves, which correlate with a diagnosis of heart failure, and a BNP level greater than 50 picograms per milliliter is the cut-off for the diagnosis of chronic heart failure.

And the mean level of baseline BNP was 1,500 in the patients in 325 at baseline.

Also as Dr. Allgren pointed out, those patients could have been hospitalized before entry into the study, and in fact, the range of time the patients were hospitalized was actually -- I'm sorry, up to 70 days.

Overall within the entire Natrecor NDA program we -- many patients were administered other

commonly used cardiac medications, and this slide simply reflects the number of patients in the program that received these medications.

As Dr. Abraham pointed out, in one of the backup slides, study 326, which was the large safety study is really the best study to look at the medications that patients were on as they entered the study, and then whether those medications were continued during Natrecor therapy.

And I will just reiterate that more than 60 percent of those patients were on Digoxin and ace inhibitors prior to entering into the study, and greater than 60 percent of the patients those medications were continued during Natrecor therapy.

So these data, again, support the fact that the experiences that occurred during the Natrecor program reflect the experiences that might be expected when the drug is used in usual clinical practice.

Now I would like to proceed to our data on mortality. These graphs show mortality rates with 95 percent confidence intervals. The bars on the left reflect the mortality rates from the six studies that

were placebo controlled only.

The blue bars represent placebo, the yellow bars represent Natrecor. In all of these studies patients were studied for two weeks, so we are representing 15 day mortality.

As you can see there is no evidence for an increase in mortality with Natrecor therapy when compared to control of placebo.

Now, the bars on the right reflect the mortality rates from the three largest studies, study 311, 325, and 326.

Here I'm referring to these studies as the long infusion studies, because these are the studies in which patients received Natrecor generally for at least 24 hours. I would just like to remind you that the grey bar here, which is marked as control, is mostly comprised of patients who were receiving another IV vasoactive agent.

Again, those patients were followed for three weeks, so we are showing 21 day mortality. And, as you can see, there is no evidence for an increase in mortality with Natrecor therapy compared to

control.

So in summary when compared to either placebo or active control there is no evidence for an increase in mortality with Natrecor therapy.

Allow me to move on to our data about the adverse event profile of Natrecor. First I will review the general adverse events which occur during the studies, and then I would like to spend a little more detail discussing the effects of Natrecor on blood pressure, heart rate, and serum creatinine.

This table shows all adverse events that were consistently reported more frequently with Natrecor therapy than control in all of the CHF studies.

As you can see here, symptomatic hypotension is the most frequently reported adverse event, followed by nausea, bradycardia in these other events are infrequently reported.

I would now like to show you these same events in the long infusion population so that you can see how these events relate to the doses of Natrecor that were administered in the pivotal studies.

From this table you can see that the only adverse event, which is clearly dose related, is symptomatic hypotension.

I would like to focus our attention, for the next few minutes, on the effects of Natrecor on blood pressure. Generally speaking an infusion of Natrecor causes dose related decreases in blood pressure. This is reflected here with this graph, which shows the mean percent change in systolic blood pressure over the first six hours of infusion.

The blue line here is placebo from the 325 study. The .015 dose reflected in yellow, and the .03 dose reflected in green show a clear dose related response to blood pressure.

Now, to understand the greatest impact on blood pressure for all patients in the long infusion studies, the next slide summarizes the minimum systolic blood pressure that was observed at any time during the first 24 hours of therapy.

Please allow us to focus on the top rows first. The top row shows the median baseline systolic blood pressure, and the range, followed by the maximum

decrease in systolic blood pressure in the treatment groups, and its corresponding minimum systolic blood pressure.

There is a couple of important points that I would like to share with you. One, you can see that the range is approximately 115, actually there were patients whose baseline systolic blood pressures were as low as 80 millimeters of mercury.

Secondly you can also see that all treatment groups experienced a drop in blood pressure, and I will just remind you that most of these control patients were on an inotrope.

Now, the bottom part of the slide shows each subject's minimum systolic blood pressure within the ranges shown here.

A couple of points here I would like to point out. First, it does appear, again, that the effect on Natrecor is dose related when you look at the numbers of patients who fall within different blood pressure ranges.

And, again, let me just emphasize that this is the minimum systolic blood pressure that was

ever observed within the first 24 hours.

The other point I would like to make is that .015 is our recommended dose, and you can see here that two thirds of the patients who received the .015 dose maintained the blood pressure above 90 millimeters of mercury at all times during the first 24 hours.

So, in sum, these data support the fact that there is a dose related response of Natrecor on blood pressure, but that patients with decompensated heart failure experienced broad variations in blood pressure regardless of treatment.

Now, I would like to focus on symptomatic hypotension only, and how it impacted clinical management. And this slide shows the greatest impact that symptomatic hypotension had on the dosing of Natrecor.

What you can see here is in the .015 dose half of the patients that experienced symptomatic hypotension had that managed with either no change in the Natrecor dose, or a dose decrease. And the other half ultimately resulted in a discontinuation of

Natrecor.

In the .03 dose there were more patients who experienced symptomatic hypotension, and more of these cases ultimately resulted in discontinuation of Natrecor.

Now, we further investigated whether symptomatic hypotension leads to serious adverse sequelae. In these complicated patients the relationship of an adverse outcome is particularly difficult.

The next slide shows a schematic summarizing the outcomes of all patients who experience symptomatic hypotension at any time during Natrecor therapy or within five hours after the discontinuation of Natrecor.

Now, in these three studies there were 336 patients, if I could just walk you through this, this is not in your briefing document. There were 336 patients enrolled in this study, 44 of those patients experienced symptomatic hypotension during this time frame, that is during study drug or within five hours after discontinuation of Natrecor.

292 of these patients did not ever have symptomatic hypotension. Of those patients with symptomatic hypotension 35 of them required no intervention, and here that is defined as the administration of an inotrope oppressor.

And 9 of those patients did require administration of an inotrope oppressor. Of the 35 patients who had symptomatic hypotension and required no intervention, 32 of these patients had no sequelae.

Over here for the patients that had the administration of Dobutamine or Dopamine 5 of them had no sequelae. That leaves 7 patients, three from here, 4 from here, that had subsequent events that might be felt to be related to symptomatic hypotension.

Now I've divided this up into the two doses, and what you can see is that overall there were two patients in the .015 group that had symptomatic hypotension at some time during the study, and later died. And there were 7 patients in the .03 group that had symptomatic hypotension and later either died or had myocardial infarction, or dialysis.

Now, in order to help you determine

whether these 7 outcomes are related to symptomatic hypotension I'd like to briefly describe what happened with each of these patients, if you will just give me your attention for a few minutes here.

Real quickly. In the .015 dose the first patient was an 80 year old man who had not responded to seven days of Dobutamine therapy, and the Dobutamine was discontinued prior to entry into study 325.

After six hours Dobutamine was resumed. Natrecor was continued until day three. This man was later made DNR within the next couple of days, and he died on day five.

The next patient is a 64 year old man who had Dobutamine added to Natrecor therapy after 24 hours, for further inotropic support. Digoxin was initiated on day 2 after his second dose of Digoxin he developed second degree avery block and hypotension, which resolved with Atropine, a pacer wire, Digibind, and discontinuation of Natrecor.

This man later related to the investigator that he had had a similar episode months previous to

that, and that was the reason why he wasn't on Digoxin.

His subsequent course include inotrope dependence, and a cardiac arrest. The patient requested discontinuation of all therapies, and he died on day four.

In the .03 dose there was a 77 year old woman with a hypertensive cardiomyopathy, who had a decrease in her systolic blood pressure from a baseline of 170 to 73 during Natrecor therapy.

The next morning routine cardiac enzymes were elevated. In retrospect, due to an elevated myoglobin upon admission, the investigator felt that the patient had an evolving myocardial infarction at study entry. This patient remained stable without symptoms, and was discharged.

The next patient, a 51 year old woman who had been hospitalized for one month for treatment of asthma, heart failure, and renal insufficiency was then enrolled into the study after one month of hospitalization.

Natrecor was administered and discontinued

after 24 hours for refractory heart failure, with subsequent trials of Milrinone, Dopamine and Dobutamine.

A repeat trial of Natrecor was also unsuccessful, and on day 5 she was started on dialysis, and this patient remained on Dobutamine through the end of the study period.

The third patient in the .032 group, a 72 year old woman had a recent aortic valve replacement and was still on a ventilator at the time of entry into the study. She received Natrecor for five days, she had a complicated course, and on day 13 developed renal failure requiring dialysis, she was discharged to home with a tracheostomy.

CHAIRMAN PACKER: Can we go through this a little bit more in less detail, please?

DR. HORTON: Sure.

CHAIRMAN PACKER: Case testimonies are not particularly very useful.

DR. HORTON: Yes. Actually, that is really the point that I would like to make, thank you for reminding me.

Because these patient narratives illustrate the difficulty of interpreting the relationship of hypertension that occurs with Natrecor, with any other drug, to subsequent events.

And I certainly cannot make that determination. In this severely compromised population bad outcomes will occur. However, if symptomatic hypotension, which does occur more frequently with Natrecor therapy leads to more frequent adverse outcomes, then the relationship would be apparent in comparative data.

So I would like to just bring up the next slide, which shows the frequency of these same events that are generally felt to be related to -- that may be related to symptomatic hypotension.

DR. KONSTAM: I'm sorry to interrupt.

DR. HORTON: Yes?

DR. KONSTAM: I actually would like to hear about those two deaths.

DR. HORTON: Okay. He is paying attention.

Real quick. A 69 year old man with a

history of multiple vascular surgeries and had a cardiac cath on the day of entry into the study. On day two he developed a femoral thrombose, requiring surgical thrombectomy. Post-operatively he never regained consciousness, he was made DNR and he died.

Lastly a 61 year old man received Natrecor for five days, he deteriorated on day 5 after Natrecor was discontinued, and received Dobutamine and Dopamine, but died on day six.

DR. KONSTAM: Thank you.

DR. HORTON: Okay.

DR. LIPICKY: We actually make people do that, because some people like to agonize, apparently Marv likes to agonize.

DR. HORTON: I think the usefulness, if there is any at all, in describing those narratives, is to shed a little bit more light on the complicated nature of the patients that have been enrolled in the Natrecor program, which is consistent with the fact that the protocols have been extremely non-restrictive, and that we attempted to enroll typical heart failure patients.

SO this slide here shows the frequency of those same events, in the three larger studies, 311, 325 and 326, within the 21 day study period. And you can see that there is no evidence for an increase of these events with Natrecor therapy than control.

Now I would like to focus our attention to the changes in heart rate that occur with Natrecor therapy. Although Natrecor is an effective vasodilator, it has not been associated with an increase in heart rate.

This may contribute to the decrease -- this does contribute to the decrease in rate pressure product, which is observed during Natrecor therapy, suggesting that maybe there is a reduction in myocardial oxygen consumption.

Bradycardia was also reported, occurring in four percent of patients in the .015 group, and 5 percent of patients in the .03 group. Mechanistically I would like to point out that Natrecor is not associated with AV node conduction abnormalities. These episodes of bradycardia generally have been sinus bradycardia with rare episodes of junctional

bradycardia.

This next slide summarizes the clinical significance of bradycardia. Bradycardia that was reported in the .015 dose was described as mild or moderate in all cases. It usually resolved spontaneously within one to fifteen minutes.

And as you can see, from this slide, in only one case did it result in a discontinuation of Natrecor.

In fact, in this case, the patient also had decreases in blood pressure, which also led to the discontinuation of the drug.

Since the .03 dose generally is associated with larger decreases in blood pressure than the .015 dose, bradycardia occurring in this dose is also more likely to occur with hypotension and to result in the discontinuation of Natrecor.

There has not been a case, in the .015 group where Atropine has been administered, but there has been one in which a patient developed a junctional bradycardia, and was administered Atropine in the .03 dose.

I would also like to just point out that there have been no serious adverse sequelae related to Natrecor induced bradycardia to date. The last specific phenomenon, which I would like to describe in more detail is the effect of Natrecor on serum creatinine.

I'm only focusing on this laboratory value because there are no other clinically significant laboratory changes with Natrecor therapy.

In addition serum creatinine is commonly affected by the disease process, itself, as well as by other acute therapies.

This slide shows us the baseline creatinine values, and I will just reiterate that there was, at least in 325 nd 326, no restriction on the level of creatinine for patients who could be included in the study.

But at the last available value, overall, there is no change in creatinine, in the change of creatinine from baseline.

However, we looked for subsets of patients who might had clinically relevant increases in creatinine,

and for this analysis we've defined that as a creatinine greater or equal to two, and at least 50 percent increased.

When we did we found that 6 and 10 percent of Natrecor patients had this elevation in creatinine, whereas only 2 percent of the control patients had this elevation creatinine meeting this criteria.

Generally these increases in creatinine were transient, and returned to baseline, or near baseline within a couple of days to a few weeks.

Information about each of these patients was provided to you in detail in the briefing document, but I would just like to show you the follow-up values for the patients in the .015 group, specifically.

So this slide shows you, generally, that there is a pattern of creatinine returning to baseline, or near baseline. I would like to point out that there were also many other reasons why creatinine might have been increased in these patients.

For example this patient here with the orange line is a patient who had a bladder outlet

obstruction and the creatinine resolved with placement of a foley catheter.

More importantly, when we looked at patients who had even more clinically significant increases, or effects on renal function, as represented by either an increase in creatinine of more than 100 percent, or patients who developed acute renal failure requiring dialysis, you can see from this slide that there is no difference in the frequency of these events compared to control.

So, in summary, Natrecor may lead to mild to moderate rises in serum creatinine but do not lead to adverse sequelae, necessarily. These changes in creatinine are biochemical changes, and not significant adverse experiences in most patients.

In addition we do not believe that this is due to a direct toxic effect of Natrecor on the kidneys, because in multiple toxicology studies, including a two week toxicology study in monkeys, there has been no evidence for any laboratory or histologic evidence of renal toxicity.

So to put these events in the context of

how they might compare to the safety profile of other agents for this indication, the prospective safety study, study 326, provides us this opportunity.

This was the largest study, enrolling 305 patients with decompensated heart failure requiring hospitalization and IV vasoactive therapy. There was no ejection fraction requirement for this study.

This was an active control study where, again, the control patients received an IV vasoactive therapy of the investigator's choice. No central hemodynamics were measured, and there was no requirement for a PA line. And that decision was left to the discretion of the investigator.

This study also allows us to understand the adverse event profile when Natrecor is administered for longer than 24 hours, since the median duration of study drug was 43 to 67 hours in the different groups.

The next slide summarizes the events that I have already mentioned. But here the frequency of these events, occurring during the entire duration, are shown.

In this study, where 102 patients were randomized to control, 58 of them received Dobutamine, 19 received Milrinone, 18 received nitroglycerin. There were 6 others who received either Dopamine or Amiodarone, and there were not enough to summarize with this type of an analysis.

Whereas symptomatic hypotension overall was more common in the Natrecor groups compared to control, when you look at the frequency of these events for specific agents, the frequency of symptomatic hypotension with Milrinone was not different from that of the .015 dose of Natrecor. It was also not uncommon with Dobutamine.

The adverse event of increased creatinine was similar to that reported in the Natrecor groups. Nausea was frequently reported with both Dobutamine as well as with nitroglycerin.

In conclusion the adverse events that may be associated with Natrecor therapy are also events which are not uncommon with other currently available agents.

In addition, these particular events

should be easily managed in a clinical setting, in which vital signs in serum creatinine are routine.

Now, up until now I've been focusing on events that have been more common with Natrecor therapy than control, but it is important to note that there were certain events that were less frequently reported with Natrecor therapy.

For example, again, in our safety study, study 326, there were three percent of the control patients experienced a cardiac arrest at some time during study drug infusion, whereas no Natrecor patient had a cardiac arrest during study infusion.

It turns out that all of those patients were Dobutamine patients. Sustained ventricular tachycardia was more common in the control group than Natrecor, and those events generally occurred with Dobutamine, as well.

Ventricular extrasystole was also less frequent with Natrecor, and mostly those were reported with Milrinone therapy. Finally, headache was most common with nitroglycerin therapy and was not uncommon with the other therapies, but generally reported less

frequently with Natrecor than the other therapies.

So when looked at in the context of how Natrecor's adverse event profile may compare to agents which are currently available, there may in fact be some safety advantages of Natrecor over these agents.

Now I would like to briefly summarize the effect of Natrecor on outcomes related to safety that were collected through the 21 day study periods.

In these studies we prospectively collected whether there was a need for emergent intubation and readmissions, we also collected length of stay. You can see here that there is no evidence for an increase in the need for emergent re-intubation, or a difference in length of stay with Natrecor compared to control.

We prospectively collected whether readmissions occurred, and whether they were for all causes, or for recurrent CHF, specifically. And, again, you can see here that there is no evidence for an increased need for hospital readmission in Natrecor versus control within the 21 day study period.

Together these data suggest that there is

no evidence for an increased need for medical interventions, generally, after Natrecor is discontinued.

In summary I have demonstrated that the safety data from the Natrecor NDA support the use of Natrecor for the short term treatment of congestive heart failure. I've shown you that the safety data base well represents the target population that would receive Natrecor for this indication.

Generally that Natrecor is well tolerated, and that the safety profile for Natrecor has been very well characterized. Finally I've showed you that there was no evidence for an increase in mortality or for the need of hospital readmissions.

Thank you for your attention, I would be happy to answer any questions you might have.

CHAIRMAN PACKER: Why don't we go onto the next presentation, and we will take questions for both, in the interest of time.

DR. HORTON: Okay. I would like to introduce Dr. Abraham from the University of Cincinnati, who will discuss the benefit risk

assessment of Natrecor.

Thank you.

DR. ABRAHAM: thanks very much. Dr. Packer, Committee members, Dr. Cohn, members of the FDA staff, it is my pleasure to offer a clinician's view of the benefit risk assessment of Natrecor for the short term intravenous treatment of decompensated heart failure.

As a heart failure specialist and clinical investigator, I have substantial first-hand experience with the use of Natrecor in such patients. This begins with my involvement in one of the first human studies of Natrecor and heart failure protocol 306, and includes my participation in the two pivotal efficacy studies reviewed today.

Based on this experience, as well as an understanding of the data presented today I'm quite enthusiastic about the benefit risk assessment for this drug.

I would like to begin with a brief review of the current status of acute heart failure. This will be followed by a summary of the demonstrated

benefits of Natrecor. I will then reiterate some of the clinically important risks of Natrecor therapy in decompensated heart failure, and before concluding I would like to describe candidates for treatment with this agent, and I will try to do all of this in about ten minutes.

This slide lists the current status of acute heart failure. I think as you all appreciate decompensated heart failure represents a major public health concern, in that it accounts for nearly one million hospitalizations annually in the United States, as well as substantial morbidity and mortality.

While current therapies are generally effective, they may be limited by adverse events, such as the risk for life threatening arrhythmias seen with the positive inotropic agents.

Thus I believe that there is a need for alternative therapies for decompensated heart failure. In this regard it is worth noting, as noted earlier, that no new intravenous drugs for the treatment of decompensated heart failure have emerged for

consideration by this Advisory Panel in more than a decade.

Given all of this another option for therapy is warranted. This slide lists the demonstrated clinical benefits of Natrecor in decompensated heart failure. In sum, Natrecor produces significant dose related favorable effects on hemodynamics while improving patient symptoms.

Specifically Natrecor significantly improves hemodynamics by decreasing pulmonary capillary wedge pressure and systemic vascular resistance.

In this regard Natrecor is a balanced vasodilator. Natrecor significantly increases cardiac output by improving stroke volume, not by increasing heart rate with no direct inotropic effect.

Finally, Natrecor produces rapid symptom improvement during therapy, as ascertained by patient and physician global clinical assessments, and by specific symptom scales.

In addition there are some ancillary benefits of Natrecor which support its use in heart

failure. For example, Natrecor has a generally favorable neurohormonal profile in that it reduces plasma aldosterone, and maintains or reduces plasma norepinephrine.

The clinically relevant risks of Natrecor have just been extensively reviewed by Dr. Horton, and are reiterated on this slide. Natrecor produces dose related hypotension, which may be viewed as excessive pharmacologic effect.

In this regard the effect of Natrecor to produce hypotension is similar to that seen with other vasodilators used for the treatment of heart failure.

Bradycardia occurred uncommonly, in less than or equal to 5 percent of subjects. And as you have seen there were no untoward sequelae associated with the incidence of bradycardia.

Finally, six to ten percent of patients experienced an increase in serum creatinine defined by an increase of at least 50 percent to a value of at least 2 milligrams per deciliter associated with Natrecor therapy.

While these increases in serum creatinine

are commonly seen during the treatment of decompensated heart failure, and have generally been attributed to peripheral vasodilation, and/or relative intravascular volume depletion, so called arterial underfilling, it is most important to note that clinically significant renal dysfunction, such as that requiring hemodialysis, was rare in the Natrecor group, and its incidence was not increased compared to the control arms of these studies.

Now, these demonstrated risks of Natrecor are certainly concerning to the clinician. But I would suggest that these adverse events are predictable, they are manageable, and as you have seen they do not produce adverse outcomes that are dissimilar, or occurred in increased frequency compared to standard or currently available forms of therapy for decompensated heart failure.

This slide presents a simplified view of a rational approach to therapy in volume overloaded heart failure patients. And I present this to you not because I'm naive and don't believe that you already understand how to treat decompensated heart failure,

but really to demonstrate a couple of points regarding what I believe is the over utilization of inotropes, and under utilization of IV vasodilators in contemporary heart failure management.

Here you can see that patients presenting with clinical congestion may be categorized into one of three groups based on an assessment of peripheral perfusion.

Patients with adequate perfusion are often well treated with diuretics, plus oral or intravenous vasodilators. Patients with frank cariogenic shock require intravenous pressor agents to support blood pressure, in addition to diuretics for extra cellular fluid volume excess.

But this large group of patients in between, with clinical congestion, and reduced perfusion, may be treated with diuretics plus either an intravenous vasodilator, or intravenous inotrope.

Now, we have seen, in the control arms of these Natrecor studies, and we know from clinical pharmacy surveys, that most clinicians currently choose to use an intravenous inotrope in these group

of patients, thus subjecting them to substantial risks, such as the risk of life threatening arrythmia.

The apparent under-utilization of vasodilators in these patients may relate to the common perception that nitroglycerin is relatively ineffective, and that nitroprusside is difficult to use, thus there is a need for alternative or additional vasodilator therapy in these patients for drugs such as Natrecor.

In this regard candidates for treatment with Natrecor are hospitalized patients, with decompensated heart failure requiring intravenous vasoactive therapy. Specifically they should be volume overloaded, and not in cariogenic shock.

This may represent the typical patient hospitalized for decompensated heart failure, according to numerous clinical benchmarking studies.

I believe this also represents the typical patient studied in this NDA with an average pulmonary capillary wedge pressure of about 25 or 30 millimeters of mercury, and an average cardiac index of around 1.8.

In addition there are other clinical considerations which you and I might consider in favoring Natrecor over other agents for the treatment of decompensated heart failure.

Given the known effects of Natrecor on heart rate, it may be particularly useful in tachycardiac patients where positive inotropic therapy is often limited.

Given the known vasodilatory effect of Natrecor, it may be preferred in patients with hypertensive heart failure, where vasodilators clearly have an established role.

And, finally, given the lack of a positive inotropic effect of this agent, it may be preferable, in those patients with a history of malignant ventricular arrhythmias, which may be exacerbated by positive inotropic agents.

In summary, Natrecor is a safe and effective form of intravenous therapy for patients with acutely decompensated heart failure. Natrecor has an excellent benefit risk profile, specially when viewed in the context of existing therapies.

Finally, Natrecor would be a useful addition to the armamentarium available for the treatment of decompensated heart failure.

I thank you for your attention, and would be happy to try to answer any questions that you have at this time.

CHAIRMAN PACKER: We will start with Marv as our primary reviewer for either of the two presentations.

DR. KONSTAM: I think I have questions for both of you, but I think I would rather start with Dr. Horton.

You know I just want to comment on the hypotension issue, in general. So we are going to expect that vasodilators will lower blood pressure, so it is not unexpected, as you are finding doses, that you are going to have a certain incidence of adverse, what is considered adverse hypotension.

So the questions that I'm going to wind up around this is, you know, can that be managed, what do we know about pharmacokinetics, and is it an ideal situation? And the ideal would be, you know, if we

could get rid of hypotension rapidly, rapid on, rapid off.

And I guess I would like some handle on that. And in thinking about it, I don't think it comes, necessarily, from the patients who had hypotension as an adverse effect, because in those patients there probably were going to be other things going on to correct the hypotension, like volume replacement, or maybe even pressors.

So maybe the only handle on this comes from the overall population, and what happens to blood pressure when you turn off the drug.

And that was shown earlier, briefly. Do you want to show that again, in terms of the kinetics of the return of the blood pressure to normal after you turn off the drug?

DR. HORTON: I think that was actually, we only showed that for wedge pressure and cardiac index. I don't believe that we have --

DR. KONSTAM: I thought I saw something pop up, but if not I would like to see it for the first time.

DR. HORTON: Actually we don't. I'm sorry, we don't have a graph showing the blood pressures returning to any particular level after the discontinuation of Natrecor in the overall population.

DR. KONSTAM: Well, you have to have that. I mean, this is going to be important.

DR. HORTON: We will get that information for you.

DR. KONSTAM: I thought that I saw a slide that had multiple panels on it, one of which was blood pressure, I thought it was in the top right-hand corner. Maybe I was --

DR. HORTON: There is a slide from study 325 --

DR. KONSTAM: There was not any blood pressure on it?

DR. HORTON: There is a slide that shows the blood pressure effect, but it doesn't continue through after discontinuation of Natrecor.

CHAIRMAN PACKER: I think the slide you are referring to is one that goes to six hours. The one that you are asking about is at 311 with the four

hour withdrawal period, at 24 hours, and we didn't see that, that was the only two variables that were put forward.

DR. HORTON: Right.

DR. KONSTAM: So I'll just editorialize again, that we are going to say, I mean, Bill made some points that this is going to be a useful agent, and in clinical practice that is going to be relevant to what.

And then the only way to get a handle on this hypotensive question is just this issue, how quickly will it go away when you stop the drug. At least that is how I'm going to evaluate it relative to other drugs, for what that is worth.

DR. HORTON: One thing I can add is that in the overall population, which is what you are asking, that at 24 hours in study 311 for example, which is the one where we do have some blood pressure information after discontinuation, the overall effect on blood pressure in that population, in the .015 dose and the .03 doses was between 5 and 10 millimeters of mercury.

And then after discontinuation of the drug the blood pressures would have gone up a little bit.

DR. KONSTAM: Okay.

DR. ABRAHAM: I'm not sure that we have the exact slide that you want, but I think it is a reasonably safe presumption that it probably parallels the same offset of effect that we see with wedge pressure or SVR.

DR. KONSTAM: Okay, right.

DR. ABRAHAM: And you have seen those slides before.

But I think even more importantly than that is the slide that Darlene showed looking at the outcomes in these patients. I think we want to know what happens on the short term, and how long does it take for the blood pressure to come back, and how they are treated.

You know, the bottom line here is that you can't really say that it produced adverse outcomes looking at hard outcomes.

DR. KONSTAM: I understand that point, and they are two separate points, and I think it is -- we

shouldn't get into outcomes quite yet. I'm just trying to get a handle on the blood pressure, the adverse effect of hypotension that we see, and what could be done.

I also would say, just commenting on the wedge pressure study. So if I'm not mistaken the return to normal and wedge pressure was hours, number one.

And number two is, it doesn't really help me all that much anyway, because wedge pressure is driven in part by intravascular volume shifts. And so that is not the same as blood pressure.

So I'm still left with that big question mark in my mind.

DR. HORTON: Dr. Konstam, I just also want to point out, unfortunately we only measured blood pressure two hours after discontinuation, and four hours after discontinuation.

So in the overall population I can only tell you those values. We have additional information about patients who had developed hypotension with repeated blood pressures in their resolution.

In one of the tables in the briefing document, under the hypotension section, for example, a third of the patients have their hypotension resolved within 30 minutes.

Unfortunately, for the benefit of the people in the audience I will just talk through this a little bit while the Committee is finding the table.

This is a summary of the duration of the event of symptomatic hypotension. Now, in some of these cases it was a single event, a transient event, as I said. In a third of the cases it resolved within a few minutes to 30 minutes.

This also includes, though, patients who had intermittent hypotension. So some of these cases did last for several hours. The entire duration of the event is several hours, although it was intermittent during that time.

CHAIRMAN PACKER: Marv, it is 65 in the briefing document.

DR. HORTON: Actually, could I have backup slide 311, please?

DR. RODEN: Are you going to tell us how

many of these patients had bradycardia and hypotension at the same time?

DR. HORTON: There were two patients in the .015 group that nad -- I'm sorry. Yes, there were two of these patients in the .015 group that had bradycardia, and seven patients in the .032 group that had bradycardia and hypotension.

DR. RODEN: Bradycardia and hypotension at the same time, okay.

DR. HORTON: Yes.

DR. KONSTAM: Right. And, again, so this useful. Again, the problem is there are other things going on. The responses to this is going on, so we don't know even what -- to what extent this represents the drug going away, and to what extent it is the responses to the hypotension going on.

DR. HORTON: Yes, that is true. This also includes those patients where there was no change in the Natrecor dose, the Natrecor was continued.

DR. ABRAHAM: In addition to confound the picture further, these patients were receiving standard medications for heart failure, so they may

have received their long acting ace inhibitor just before their episode of hypotension, and so you really cannot discern the offset effect.

This is not a clinical pharmacology study.

DR. KONSTAM: So I'm back to where I started from, which is the only thing that I can think of that is really going to help me on this, is looking at some population data and stopping the drug, and seeing what happens to blood pressure in a controlled setting. That is really the only thing I can think of that is really going to help me.

DR. HORTON: I do have late breaking news on that point, from my competent colleagues in the second row.

In study 311, after 24 hours, patients in the .015 group had a mean decrease in blood pressure of minus six milliliters of mercury. The .03 group was minus 3.3. And in the .06 group, which is a dose we are not recommending, it was minus 9 dose related effect.

Two hours after discontinuation, the first time point that we measured it in the overall

population, the results are plus 2 millimeters of mercury in the .015 group, so it is back to baseline; minus 3 in the .03 group, and minus 6 in the .06 group; and then at 4 hours the numbers are zero, minus 3, and minus 2.

So certainly within two hours the numbers are, the blood pressures are back to baseline. But that likely happened before that.

DR. KONSTAM: Well, I don't get that exactly. I mean, they got back to baseline in the .015 group, but not in the other groups, right?

DR. HORTON: That may be true, yes.

DR. KONSTAM: Okay. Can I ask about the creatinine question, one question I had. Do you have any information about relating creatinine to blood pressure effects? I don't know, can you get a handle to what extent it is being driven by blood pressure?

DR. HORTON: I do. Can I have backup slide 335, please?

Actually to answer two parts of this question, the first part of this slide looks at the risk of increased creatinine according to baseline

systolic blood pressure. And you can see that patients who have a baseline systolic blood pressure of less than 100, and there are 50 of those patients in the all Natrecor group, there is no increased risk for those patients of developing increased creatinine. That is one point.

Secondly, if you look at patients who had a systolic blood pressure lower than 85 at any time during the first 24 hours, there again is no apparent increased risk.

DR. KONSTAM: Okay. Now, I have another question, which is plasma proteins, you didn't talk about that at all. There is some evidence that I see in the data set that plasma protein levels are going down significantly in the treatment groups.

Do you want to comment about that?

DR. HORTON: I'm sorry, I don't have that information in front of me.

In our analysis the minimal changes that were seen with plasma proteins were not clinically significant. I don't really have any further comment.

DR. KONSTAM: Well, in the medical

reviewers -- in the Agency document on page 157 and 158 there are tables related to decreases in total protein concentration. The table on the bottom of page 157 is the all heart failure trial, and on top of 158 is the long infusion trials.

And in the Nesiritide group, for example, taking one piece of data, last available on or before day 2, I guess, control 14 percent, Nesiritide 34 percent, P equals .001.

And then, similarly, taking the long -- I mean, that is just one piece of data, we can look at the whole table. Long infusion trials similar sort of data. Last available on or before day 2.

For example, in the Nesiritide .015 group, 47 percent of the patients, compared to 13 percent of the controls, P equals .038.

So it seems like it is happening.

DR. HORTON: Right. Could I see backup slide 348, please?

You are referring to patients who, when you say 48 percent of the patients you are referring to --

DR. KONSTAM: Well, I'm just reading from the table. I mean, somebody else can --

DR. HORTON: But it is 8 percent of patients that had a change from normal to low. What is it?

DR. KONSTAM: I don't know.

DR. HORTON: I think it is difficult --

DR. LIPICKY: You might ask the reviewer why he thought it was reasonable to calculate P values here.

DR. THROCKMORTON: I didn't do that.

DR. LIPICKY: Who did that?

DR. THROCKMORTON: The sponsor. Those were looking at -- those are shift table analyses looking at changes from normal value at baseline to, in this case, abnormally low serum protein values, either total protein or albumin.

And that is data that was prepared by the sponsor.

DR. LIPICKY: Do you know why you duplicated the P values, why did you record them?

AUDIENCE: Completeness sake.

DR. LIPICKY: He did a very thorough review, right?

DR. HORTON: I will just bring your attention to the slide here, which actually talks about the magnitude of the changes that were seen in the two top labs are protein and albumin. And this is at the last available laboratory value representing the change from baseline, which is minus 0.1 in the three treatment groups.

DR. KONSTAM: I don't know, this is, you know, one of the points that was made by the medical reviewer. It did strike me as interesting, intriguing, and maybe of some potential concern relative to what the drug is doing.

And I guess the general question, I mean, maybe I can ask, you know, open it up in terms of the general mechanism with regard to the drug, whether there is an increase in vascular permeability, and an increase in third spacing going on.

DR. LIPICKY: You might ask Doug whether that is what he implied.

DR. KONSTAM: Doug, is that what you

implied?

DR. THROCKMORTON: Yes, in fact that was the thing that I did raise. That is something that has been suggested in several papers for atrial naturietic peptide, and was in fact something that I thought was a possible mechanism for BNP as well.

CHAIRMAN PACKER: Do you have questions for Bill, as well?

DR. KONSTAM: I do. Bill, where are you? I can't see you. I enjoyed your presentation. I mean, I guess you made one comment nitroprusside is difficult to use. Why do you think nitroprusside is difficult to use?

DR. ABRAHAM: I think, and I want to be very carefully -- I wanted to state this very carefully. I think what I said was that nitroprusside is seen or perceived to be very difficult to use.

In fact, I readily use nitroprusside for the treatment of these patients. But it is interesting that if you look at the control arms of these Natrecor studies, nobody chose to use nitroprusside as the control agent.

And I think that that is fairly reflective of common practice. But I would suggest that that may represent under-utilization of a good therapy.

DR. KONSTAM: Well, let me ask you the question. You identified patients in whom you would consider using Nesiritide. Can you tell me what is the patient profile that if you had in front of you right now you would prefer to use Nesiritide over nitroprusside?

DR. ABRAHAM: I think in general, with experience with both agents, that I would probably favor using Natrecor in the patients that I would consider for nitroprusside.

And the reason for that, and I want to be very careful about making comments which are evidence based and data driven, but I do believe that the overall profile of a naturietic peptide, in general, and of this agent in particular, has some effects which are desirable to go beyond strictly a vasodilator.

I think that there are favorable effects on neurohormonal profile, there clearly are favorable

effects on heart rate and rate pressure product. And while we can debate and talk about responders and non-responders, there appears to be, in most patients, a generally favorable effect on the kidney.

Although we have seen in all circumstances where we treat heart failure we can also go the other way, and we can cause pre-renal acidemia and we can do that with this agent as well.

DR. KONSTAM: Well, I'm just commenting. I mean, I respect your conclusions, but I don't see any of them really being driven by the data set here.

I mean, am I missing something?

DR. ABRAHAM: Well, I think they are driven in part by this data set, but again I've taken a little liberty and also considering the general fund of knowledge surrounding the use of naturietic peptides in these patients.

DR. STEVENSON: I think the majority of the use of nitroprusside in the United States is represented within this auditorium here. I'm clearly a great proponent of it, as you know.

However, I've been increasingly distressed

that our colleagues do not use it. There is considerable concern about Nipride toxicity due to cyanide. Whether or not it occurs as often as everybody worries about it, and I'm really distressed at the fact that inotropic therapy is beginning to really take over in most of our colleagues' practices, due to concerns that they cannot use nitroprusside, and I feel we really need an alternative.

CHAIRMAN PACKER: Dan?

DR. RODEN: Something you said reminded me of a question I wanted to ask. And that is, you attributed the effect of Nesiritide on naturietic peptide action. And I want you, or somebody from the sponsor to speculate about what the mechanism of action of this compound really is.

You told me earlier that you didn't think it -- you thought it was a misnomer to call it a naturietic peptide. So I would like some sense of what it does at the biochemical, or at the fundamental cellular level to achieve these actions.

And maybe you can -- you mentioned also that it had -- produces a favorable neurohormonal

profile, but we didn't see any of those data, and I would like to see some sense of what it does to catecholamines, and other measures of neurohormonal status, if you have them.

DR. ABRAHAM: I believe we have some backup slides on neurohormonal profile, and perhaps while we locate this we can comment on mechanisms of action.

There are representatives from the sponsoring company here, that have done some of the basic cellular physiology with the compound, and I would invite them to come to the microphone, if they wish.

But basically this effect is mediated via cyclic GNP, as the intracellular second messenger. And so you would presume that the typical effects that cyclic GNP has, would be seen with this agent.

DR. PRATTER: Yes, I'm Dr. Andrew Pratter, and I've done the pre-clinical pharmacology for the program, for SCIOS, and we have studied in cells, and in animals, the mechanism of BNP.

And it is well known in terms of receptor

mediated actions that it is interacting specifically in a high affinity manner with what is called the guanalose cyclase A, or the GCA particulate guanalose cyclase receptor.

That is very clear. Receptor knockout studies in which that receptor is specifically taken out of mice, they no longer vasodilate in response to BNP. And David Garber in Texas has shown this very nicely.

With regard to what it is doing in vivo, we know reproducibly, when you give this to an animal, that the vasculature, we get vasodilation. You can see reductions in systolic blood pressure, which is very consistent with the decrease in pre-load.

Before it was mentioned, the issue of blood volume, and whether you get a hematocrit shift or not. Whether this is in animals, or in clinical trials with ANP, that is a very hit or miss. Sometimes you see it, sometimes you don't. It is a very subtle effect, and it is not quite clear if that contributes to the hemodynamic actions of BNP or ANP.

Anything else?

DR. RODEN: The neurohormonal actions?

DR. ABRAHAM: Let's go to backup slide 206.

DR. RODEN: And what about the mechanism of the effect of -- on Aldosterone?

AUDIENCE: It is known that there are GCA receptors at the adrenal gland. You can -- in isolated cell preparations you can inhibit with BNP, angiotensin II, or ACTH induced aldorelease.

DR. ABRAHAM: I think that there is compelling data in the literature supporting this as a class effect. There is data for other naturietic peptides, such as ANP and urodilantin, as well as this data, and other data.

DR. RODEN: We should stop calling them naturietic peptides.

DR. ABRAHAM: These peptide hormones including BNP. So this data comes from study 325 shown on the top are effects on plasma norepinephrine, shown on the bottom effects on plasma aldosterone at baseline, and at six hours for placebo. And the two main dose groups of -- and the two dose groups of

Natrecor used in the study.

And, again, you will see that in regard to plasma aldosterone, and this is why I was careful to say that plasma aldosterone is significantly reduced, because it is, and it is reduced in this as well as other studies.

And I was also careful to say that plasma norepinephrine is maintained or reduced, because in these large studies, plasma norepinephrine was not statistically reduced.

In my own protocol 306, which was a single center study, or perhaps the measurements are done a little bit more carefully, we did see a significant reduction in plasma norepinephrine.

And in any event, both observations are consistent with published literature of these peptide hormones.

CHAIRMAN PACKER: Ileana and then Joann.

DR. PIÑA: I have a few questions for Dr. Horton, if she could come back up.

DR. LIPICKY: While she is coming up, did that answer help you, Dan?

DR. RODEN: Yes.

DR. LIPICKY: Yes?

DR. RODEN: I think so. I guess my decision about whether this compound should be approved for marketing or not didn't depend on that answer.

But, nevertheless, I wanted to know, because I think we shouldn't be approving compounds whose mechanism of action is not thought about, or completely misunderstood, or not well understood.

Because that is sort of asking for trouble later. And if you have some sense of why it works, then you might have some sense of what the toxicity might be later.

CHAIRMAN PACKER: Don't go there.

(General laughter.)

CHAIRMAN PACKER: We could spend three days on this.

DR. RODEN: We will discuss it at lunch if Milton lets us.

DR. PIÑA: Dr. Horton, let me refer you to your slide number 47, where you have the list of

medications given during Natrecor infusion. And I heard you use the 60 some percent for ace inhibitors, but 186 of 505 is not 60 some percent, and I don't know what this refers to.

DR. HORTON: Sure. Let me clarify. This is actually the numbers of patients who received these medications during Natrecor therapy in the entire CHF program, so it is in all eight studies.

And, in fact, in most of the earlier studies, these medications are restricted. If I could have slide 267, I think this will help.

Slide 267, these are the numbers and percentages of patients who received these medication before entry into study. So basically those are the medications that were used within the 24 hours before receiving study drug.

And then the column on the right is whether those medications were administered during Natrecor therapy.

And first you see that there is a very high -- well, more than 60 percent of patients, for example, receiving Dig and ace inhibitors, and it

appears that they continue to be administered those medications on -- during Natrecor therapy.

A similar patterns with non-IV nitrates, with the antiarrhythmics and with diuretics.

DR. PIÑA: That is in one study, that is in 326?

DR. HORTON: Yes, that is the largest study that studied 305 patients, and it is the one study which is really the real world study.

DR. PIÑA: My other question refers to your slide number 55 and 56, we are going back to this management of symptomatic hypotension. You have, on slide 55, you have 37 patients, and on slide 56, where you are going through the breakdown of symptomatic hypotension you have 44?

DR. HORTON: Yes.

DR. PIÑA: What is the difference in those two populations, number one. And number two, do you call intervention for hypotension actually the administration of oppressor, or is an intervention simply withdrawal of a Natrecor drug?

DR. HORTON: Right. Again I would love to

clarify. In slide 55, this slide represents the patients that had symptomatic hypotension in the first 24 hours. So -- and then this next slide represents the numbers of patients who had symptomatic hypotension at any time during Natrecor therapy, which may have been up to nine days, or within five hours after it was discontinued.

So there are more events, there are 44 events, as opposed to the 37 events which were observed in the first 24 hours.

So, number one, that tells you that most symptomatic hypotension is identified within the first 24 hours. But this slide really is more comprehensive and allows for us to really say what happens to all patients who develop symptomatic hypotension during this time frame.

Now, the previous slide only talks about the greatest effect on Natrecor dosing, whether there was no change, whether it was decreased, or whether it was discontinued.

This slide, in contrast, when I talked about intervention, I -- the definition of

intervention is the administration of an inotrope or oppressor in response to the symptomatic hypotension.

Patients who had Natrecor decreased or discontinued are not represented here. They are represented on the slide, but they are represented as no intervention.

DR. PIÑA: So, in other words, if I understand this correctly, the 37 patients had their blood pressure abnormality within the 24 hours, that means there are seven patients that became hypotensive after?

DR. HORTON: After 24 hours.

DR. PIÑA: And off drug?

DR. HORTON: No, it would have been after 24 hours, and within five hours after Natrecor was discontinued. So it might have happened in patients who got drug for three days, sometime after 24 hours.

I included the symptomatic hypotension that occurs within five hours because I wanted to be fair, and to be -- take a conservative approach, that is to implicate that hypotension that might happen within five hours after Natrecor is discontinued could

still be potentially related to Natrecor therapy.

DR. PIÑA: Thank you. And I have a question for Bill.

Bill, you've been talking about the real world. In the real world most patients are not adequately treated, even with good old ace inhibitors, much less anything else.

And one of the reasons that we would use a short term compound, other than to obviously make the patient feel better, and you have them in the hospital for a reason, because they are ill, is to have the opportunity to up-titrate other drugs that you will eventually hopefully put them on, and send them home.

Where do you see the drug of this agent for that real world use?

DR. ABRAHAM: Yes. I think that this agent can also be viewed as a bridging agent. And, in fact, we need to think of all IV agents for the acute management of heart failure as bridging agents. Because as we have demonstrated, in lots of clinical pharmacology studies, if you don't do anything else

when you turn the drip off, the patient goes back to their decompensated baseline.

I believe the experience in ace inhibitor treated, and other vasodilator treated patients is substantial, and that as is typical of our practice, we start low and we go slow, and take an incremental approach to try to wean patients off of their dependence of the intravenous agent, and on to an adequate oral medical regimen.

That is not to say where there may not be some instances, particularly in the low blood pressure patients, where we might have to resort to an inotrope as a way to bridge them to that oral therapy.

I don't think all patients will be successfully treated with, or bridged to oral therapy by a vasodilator in general, or Natrecor in particular.

CHAIRMAN PACKER: You had a specific follow-up on that, or this is for later?

DR. PIÑA: Specially since I'm not bowled over by diuresis here, either. And, obviously, there was more conservative views of diuretics while the

drug was going on, but it is certainly not addressing the volume stats.

CHAIRMAN PACKER: Ileana, you had another follow-up? We will go to Joann and then to Jay.

DR. LINDENFELD: Clarification. In your real world study 326, despite the use of Dobutamine there was no difference in heart rate, is that correct?

DR. HORTON: I am sorry, say that again?

DR. LINDENFELD: There was no difference in heart rate at six hours, or 24 hours?

DR. HORTON: Despite the use of Dobutamine, did you say?

DR. LINDENFELD: In the real world group, in the control group.

DR. HORTON: I'm sorry, I'm not understanding your question. Are you asking me if --

DR. LINDENFELD: Well, Bill made the comment that there may be a decreased rate pressure product with this drug, and certainly pressure is less. But it didn't appear to me that there was any difference in standard care versus Nesiritide and

heart rate.

DR. HORTON: The information that was shown comparing the effect on heart rate was from a placebo controlled study, not a Dobutamine control study.

DR. LINDENFELD: I think on page 76, standard care versus Nesiritide at 3 hours, there is no difference in heart rate versus your standard care in this drug. So I don't think we can say much about heart rate being of benefit here. Page 76 in the FDA book, bottom of the page.

Blood pressure is less, certainly, but we can't say too much about heart rate, I don't think you are comparing to a real world look.

DR. HORTON: That is correct that there is no change compared to IV vasoactive therapy overall, but a little more than half received Dobutamine, correct.

DR. LIPICKY: So when we pick out patients, I'm not sure we can use that.

Just help me with, in study 325 we are still interested in creatinine. In study 325, within

the first six hours, 14 and 17 percent of the two Nesiritide doses required some specific intervention for renal insufficiency? That is what it says on page 65, zero percent in the placebo group, 6 patients are 14 percent in the low dose, and 7 are 17 percent in the high dose that required some specific intervention short of dialysis.

That is a little bit of a concerning number in just six hours.

CHAIRMAN PACKER: Can you repeat those numbers again, Joann?

DR. LINDENFELD: Yes, it is in study 325, this is on page 65, medical intervention without dialysis, such as IV fluid boluses and medication changes were required in 0 of 42 placebo patients, 6 of 43 or 14 percent of the low dose, and 7 or 17 percent of the higher dose.

CHAIRMAN PACKER: Is this the one that has the nominal P values, .033?

DR. LINDENFELD: It just says requirement for intervention due to worsening renal failure. That is throughout. I wonder why it was higher here, and

then --

DR. GROSSBAR: I'm just trying to correct an earlier comment. My friend Dr. Massey informs me that on the Dobutamine question earlier that there was an increase in heart rate in the Dobutamine group by several beats per minute. The P value was .05 something, so it may not be an overwhelming proof of that effect, it is not proof of no effect.

DR. LIPICKY: So I just want to get back to this point about in 325 why we saw all this need for intervention for renal failure, and we didn't subsequently?

This is a fair number of patients that required specific intervention.

DR. ALLGREN: I believe you are talking about the table in study 325 of people giving interventions for the rising creatinines, such as fluid boluses or maybe making a change in the medication.

I think that is reflecting the issue that Dr. Horton had talked about with regard to the rising creatinines. I believe if we look at that same

intervention, we are trying to pull it up for study 326, it was fairly balanced across the groups in that study.

DR. LINDENFELD: And then just --

CHAIRMAN PACKER: Before we leave that, just so we can clarify, 326 was active control, so if the active control had an adverse effect on creatinine, one would not pick that up. So 325 is placebo control, the data I think that Joan --

DR. ALLGREN: Really only for the first six hours in that study.

CHAIRMAN PACKER: Right. I guess that the data -- this is from Dr. Throckmorton's review. Also it is a two percent incidence of interventional placebo, 14 percent on low dose, and 21 percent, actually, on high dose.

DR. ALLGREN: I just want to be sure it is clarified that those are interventions throughout day 21 in the study, it is not talking about just the first six hours.

CHAIRMAN PACKER: I see.

DR. ALLGREN: In both studies 325 and 326.

DR. GROSSBAR: And except for the first six hours, in 325, all those patients were crossed over to typical standard therapies. So it is -- it is not a six hour event, and it is cumulative, and it is not against the placebo, it is generally against the population.

DR. LINDENFELD: Just to clarify, how often was creatinine measured in 325 compared to 326, were they the same?

DR. HORTON: They were the same, they were measured daily through the duration of pre-renal vasoactive therapy.

DR. LINDENFELD: And then a question about sodium. This comes up to how effective is this drug, in some patients creatinine is increased, and I was concerned to learn that along with that there is a trend, a pretty good trend for sodium to be decreased, particularly in the long term study.

It bothers me a little bit in a drug where we think that although we are not going to claim that it has naturietic actions, that there is this sort of suggestion that this is great for the kidneys.

On page 151 of the briefing document, there is a trend at least towards a dose dependant decrease in mean serum sodium, and in the Nesiritide groups.

DR. HORTON: Could I have backup slide 346, please? This slide looks at the overall changes from baseline at the time of the last available lab value. And my conclusion, from this slide would be that there is no clinically significant difference, and the difference is not different in the treatment groups.

DR. LINDENFELD: We've got different numbers, I think, do we, or are they -- the table I'm looking at is in the bottom of 151, where we show for control minus .4 sodium, minus .8, minus 1.2, and minus 1.8 over the three doses of Nesiritide.

One is actually day two and one is last available, also. So through day two there appears to be at least a fairly substantial trend with dose --

DR. ABRAHAM: I guess I might view this data similarly to how we are looking at the naturietic effect of this agent. In fact, in some ways, it

suggests that there may be a modes naturietic effect, because this is what we see routinely when patients are given standard naturietic or saluretic agents, and replace some of their volume loss with free water.

But I don't want to make that leap of faith and come to that conclusion except to say that in some ways, you know, perhaps this data is not fully reliable, or we are making more out of it than we should, given such a heterogenous response. It depends on when you look, it depends on which study you look at, whether or not you even see this effect on sodium.

DR. HORTON: Actually, if I could have backup slide 305, please?

Given the different time points, the different populations that we are looking at, this is a measure of the clinically significant adverse events that the investigator reported. The fourth line there is hyponatremia, so these are adverse events related to laboratory values.

And you can see that there is no difference, no clinically -- no difference in the

groups, but in fact there is less hyponatremia reported. Our conclusion would be that there is an insignificant effect, that there is no effect.

DR. LIPICKY: There is no creatinine up here?

DR. HORTON: I already gave you that information, that is in 6 and 10 percent of patients in the Natrecor groups.

DR. LIPICKY: Those point estimates are smaller than whatever it is, standard deviation, or standard error that is next to it. If I looked at that table I would have said there was nothing there.

Why do you really think there is something there?

DR. LINDENFELD: Well, there is a comment here that there is a trend towards --

DR. LIPICKY: Well, ignore the comment, look at the numbers.

DR. RODEN: I hate to agree with Ray, but if the serum sodium in a patient with heart failure goes from 132 to 131, I don't think that is clinically significant. I don't think that tells you that it is

a naturietic peptide, either.

DR. LIPICKY: But this is not a clinically significant argument. I think these are just numbers.

DR. PIÑA: And I don't think you can make any statements about iso or hypotonic volume, because the volume didn't change much in any of these patients, including the intake, which was pretty constant throughout the whole time.

CHAIRMAN PACKER: Jay?

DR. ABRAHAM: I apologize for speculating on the mechanism of that.

CHAIRMAN PACKER: Jay?

DR. COHN: I would like to get back to the concomitant therapy issue, because in the real world, so called real world study that you've shown us, ace inhibitors were given to only 62 percent of the patients prior to intervention with Natrecor.

Diuretics were being used in about 82 percent, I think, which strikes me as somewhat surprising that it isn't 100 percent, since these people are obviously all in severe enough heart failure to require hospitalization, and yet 18 percent

of them weren't getting diuretics, and 38 percent weren't getting ace inhibitors.

It gives you a unique opportunity, though, despite the fact that I'm trouble by what was pre-existing therapy, to look at the relationship between Natrecor side effects, and adverse events, and co-therapy. That is, is there any evidence that those patients on an ace inhibitor had a greater incidence of hypotension, and in fact we would like to think that 100 percent of patients who get subjected to this therapy are going to be on an ace inhibitor, and the incidence of that, therefore, might be higher.

Also the incidence of use of beta blockers was, of course, very low in this study. And yet that may become a much more common phenomenon in the future that these patients are going to come in being on a beta blocker.

So I would like to hear something about interaction, if you will, with co-existent therapy for heart failure, especially in significant doses, and maybe some explanation of why only 62 percent of these people, in what I assume were pretty formidable

centers, it may not be the real world, but it is probably the real world in the centers in which you've done this trial.

Why so few of the patients were on what we would consider to be optimal therapy for heart failure?

DR. HORTON: Yes. I think I can clarify that point. To understand the limitations of how that data was collected, medications prior to study, and the slide I showed you, the 62 percent and 82 percent, those are actually medications that were administered within 24 hours before entry into the study.

So it was not a question of what is the patient's chronic cardiovascular regimen. And, in fact, patients who were non-compliant with the regimen would not show up in that table, because if they did not receive the medication, or if there was not evidence that the patient received that medication, in the medical record, it is not reflected on that slide.

DR. COHN: So you really don't know what the therapy was in the stable period of time before the patient entered into the trial?

DR. HORTON: I know that they had to have received at least 62 -- at least 62 percent of patients had to have been receiving an ace inhibitor, and at least 82 percent of patients had to have received a diuretic during the 24 hours.

DR. COHN: But it may have been much higher than that, obviously?

DR. HORTON: Yes.

DR. COHN: If an ace inhibitor, long acting ace inhibitor had been used 25 hours before your study, I assume it wouldn't show up, and yet this patient is still potentially having an effect from the ace inhibitors, is that right?

DR. HORTON: That's correct.

DR. GROSSBAR: Darlene can speak to the interaction question, and I don't want that to get lost. But it would probably be even problematic to characterize a patient who is on Lasix but not taking it.

Unless heart failure has changed in the 15 years since I was a house officer, that was a very common reason why people ended up in the hospital,

they simply stopped taking the medicines they were on.

So I don't know if it is a commentary on the center, or on the population of patients who show up at a center. And all we wanted to know was what their status was beforehand, I don't know what we would do with information that said that they were on Laxis but not taking it.

DR. COHN: But it would be very hard to get into an emergency room with worsening heart failure and not get a dose furosemide in the emergency room.

So the fact that they weren't getting a diuretic prior to entry into this protocol is still somewhat surprising, even if they were non-compliant outside.

DR. GROSSBAR: But we do have interaction information which we --

DR. HORTON: Could I have slide 300, please? This slide shows the four adverse events that are consistently reported more frequently with Natrecor, and their association in patients who either were receiving an ace inhibitor, or not receiving an

ace inhibitor.

And what you see here is that there may be an increase in symptomatic hypotension with concomitant administration of an ace inhibitor. And that is consistent with the fact that both are vasodilators, and that they should be used with caution, and that certainly blood pressure should be monitored, specially when the peak effects of the concomitant medication are expected.

But you also see that they are generally well tolerated with 90 percent of patients who are receiving an ace inhibitor, not experiencing symptomatic hypotension.

CHAIRMAN PACKER: Any other questions, Jay? I guess not. Does anyone else have any questions for either of the two presentations? Cindy?

DR. GRINES: I just have a real quick question about the creatinine elevations. And you had shown a slide demonstrating that they weren't more frequent in patients with a systolic blood pressure of less than 85, but for heart failure patient that might be pretty normal.

And I wondered if you had any information with regard to patients with profound hypotension, perhaps those less than 70, or patients who had sustained hypotension for more than a couple of hours?

DR. HORTON: I'm sorry, we didn't look at it in that way.

CHAIRMAN PACKER: Let me ask, and is to either of the two speakers. The proposed labeling for this drug actually suggests that the word rapid be included in the description of the effect of the drug on both hemodynamics and symptoms.

In a conventional intensive care unit setting, physicians are used to thinking of rapid as minutes. And all the drugs that Bill mentioned are agents that work very, very quickly, either because they intrinsically work very quickly, or because they are given as a bolus followed by an infusion.

So that almost all the agents that we used in an intensive care unit work within five minutes, ten minutes. And peak about that same time.

This is an agent that works, or appears to work more slowly, and that peaks at three hours, and

that people shouldn't increase the dose of this drug in an interval less than three hours.

Do you think the word rapid is appropriate?

DR. HORTON: Yes. Your reference to other agents that work within minutes to a half hour or so, must obviously be in relation to its hemodynamic effect. And, in fact, the onset of action of Natrecor is within about 30 minutes, so you can see decreases in wedge earlier than that. But statistically significant are seen in 30 minutes in the early studies.

When we got to the pivotal studies the first measurement of central hemodynamics was either one hour, one and a half hours in the two pivotal studies.

At both of those time points the effects on wedge are statistically significant, and that was the first time point that was measured.

With regard to symptoms, the first I mean point that we mentioned symptoms was at six hours.

CHAIRMAN PACKER: I don't disagree with

when you collected the data, I'm just wondering whether in the conventional sense physicians will think that rapid means something other than what the data base would support.

DR. HORTON: I think Bill should answer that one.

DR. LIPICKY: I think that word will disappear, Milton.

CHAIRMAN PACKER: Okay. You don't have to answer it, Bill.

DR. ABRAHAM: Okay.

CHAIRMAN PACKER: And one related question to the proposed wording for labeling, the sponsor is proposing initiation of therapy at an infusion rate of 0.015, and I believe that the wording being proposed by the sponsor is if a further hemodynamic effect is desired, that the dose would be then increased to 0.03. Is that correct?

DR. HORTON: Up to point zero --

CHAIRMAN PACKER: Right, or up to. How would one know how to do that if you didn't measure hemodynamics, which is what you are saying physicians

need not do?

DR. HORTON: Right. Within the context of routine heart failure clinical management, the way that these, as you know, I'm embarrassed to be saying this to you, that the way these patients are managed is that your goal is to achieve symptom improvement and rapid hemodynamic improvement.

There are patients that you don't have central hemodynamics for which you are fairly certain, by a number of clinical measures, peripheral circulation, dyspnea, capillary refill, jugular venus distension, that you know that you haven't achieved the hemodynamic results that you aimed to do.

And so you may titrate the agents that you now have currently available to you.

CHAIRMAN PACKER: It can't be symptoms, because you haven't shown a dose response on symptoms.

DR. HORTON: Right. You are absolutely right. It is clear that there is no dose response in symptoms, although both doses do cause significant symptom improvement by six hours.

This is really a question that is left up

to individual physicians. And if for some reason they want to achieve a better hemodynamic endpoint, and the drug has been tolerated at .015, that those patients, that physician should be allowed to increase the dose to achieve that.

CHAIRMAN PACKER: I have no problem with allowing physicians the -- to use their judgement in this regard, which I think inevitably they would do. It is just that there seems to be some inconsistency in thinking through the process of what would lead a physician to do that if, as you indicate, or as you suggest, they need not use invasive hemodynamic measurement, the clinical responses are not dose dependent.

How would someone not using the Swan-Ganz catheter ever make the decision to increase the dose?

DR. GROSSBAR: I believe that our position in making that recommendation was simply to reflect the information that we had provided, and that recognizing that there are many patients who are monitored with PA catheters, and whose wedge pressure is followed and managed with current agents, whether

it is nitroglycerin, or nitroprusside, or what not, we wanted to at least allow the opportunity for those patients to be aware that there was a possible increased hemodynamic benefit, and to characterize the potential increased hemodynamic risk, and not to exclude that possibility by virtue of labeling, and have it left to a situation where people say, none of you people pay attention to the label, anyway, we shouldn't worry about it.

So we are simply characterizing it, if you manage patients this way, this is the way to manage them.

DR. LIPICKY: I guess just an information thing. Is there some relationship between the jugular venus pressure and the pulmonary capillary wedge pressure?

CHAIRMAN PACKER: I will just take a shot at this. I think the answer is, in general there may be. It is not consistent because, in fact, the dynamics on the right and left side may be different, and that may be particularly true in acute ischemic states.

So I think the answer to that is, you know, sometimes there is, but I'm also struck by the fact, if I remember, right atrial pressure, which is what jugular venus pressure is reflecting, was measured in the trials, but the effect on pulmonary wedge pressure at 24 hours was more striking, and more consistent.

DR. COHN: I think the answer to that question is that in chronic heart failure, that the two do track together. In acute ischemic events they clearly do not.

CHAIRMAN PACKER: For those who aren't involved in the area of heart failure, the discussion which is occurring now is a familiar one to many of us.

DR. STEVENSON: We looked at 1,000 patients, and the correlation at baseline between atrial compression wedge is .67, the correlation of the changes in the two was .65, so it is not exact, it does track together.

DR. ABRAHAM: I guess I'll just add, and all of you know this better than I do, it is really

the whole package that you are looking at here, and we call that clinical judgement. It is not just the neck veins, it is not just the blood pressure, it is not just the symptoms, but it is the whole package.

And I think titratability of any drug just acknowledges the fact that when we look at averages in clinical trials, we also need to acknowledge that individual patients respond individually to any drug, or any given dose of a drug.

CHAIRMAN PACKER: Dan?

DR. RODEN: This is a question that will come up in the questions, and traditionally we don't ask your advice during the questions, so I would like your advice to me now.

Defend the lack of a bolus, and defend the fact that the starting dose is a dose that looks like it is at the top of the dose response curve for at least some measures in some studies. And shouldn't the starting dose, therefore, be lower?

DR. ABRAHAM: Yes. There are two studies that I fall back on. And, again, this is from the clinician and clinician investigator standpoint.

And those are the early phase II studies, 306 and 307, looking at infusion without a bolus, and looking at incremental doses across a dose range, starting with a low dose below the current recommended doses.

And I think you do see a dose response in that study, which sort of defines the low to the high end of the dose response curve.

And, again, in our own work, from protocol 306, the onset of action to significant reduction in wedge pressure is seen within 15 to 30 minutes without a bolus.

And so my impression is, and this is not data driven, these are small studies with small numbers of patients totaling 36 altogether, is that the bolus dose is not necessary, and we have defined a reasonable dose range.

CHAIRMAN PACKER: We will hold here. I'm afraid that my watch stopped a while ago. So I didn't realize what time it was. We will take 20 minutes, hopefully no further lunch break and reconvene at that time.

(Whereupon, at 1:30 p.m. the above-entitled matter was recessed for lunch.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:00 p.m.)

CHAIRMAN PACKER: No introduction, but simply go forward to question number 1.

Trials 311, 325, 326 received the greatest attention from the sponsor and the reviewers, and received the greatest attention at today's meeting. Were the results of the five other trials, these were smaller, pilot trials, sufficiently consistent with the results of these three that today's discussion can be limited to 311, 325 and 326, or are there disparities that need to be reconciled?

We will call on our primary reviewer to summarize his thoughts and see if the Committee agrees or disagrees.

DR. KONSTAM: I don't see any disparities with the other studies that raise attention.

CHAIRMAN PACKER: Does anyone disagree?

(No response.)

CHAIRMAN PACKER: Question number 2, how should the patient population of trials 311, 325, 326 be characterized? Was it a typical population of

patients with chronic congestive heart failure, sufficiently decompensated (from any cause) to require hospital admission for the treatment of that decompensated?

Marv?

DR. KONSTAM: Yes, I think that is a little difficult, and we have been through discussions about this. I think it is clearly a population of patients, both 311 and 325 clearly are populations who have -- who are sick with heart failure. I think 325 all we really have to go on in this is the fact that entrance criteria required this phrase of decompensated sufficiently to require intravenous therapy.

I, you know, it is not precisely the population that we most might want to use the drug in, but I'm not sure, honestly in my ow mind, that we can do any better than that.

So I don't know how to characterize it any better than that.

DR. RODEN: Marv, are you referring to acute MI patients when you say that, or just --

DR. KONSTAM: I'm sorry, I don't --

DR. RODEN: When you are talking about from any cause.

DR. KONSTAM: No.

DR. RODEN: Are you including acute MI patients?

DR. KONSTAM: No, I'm sorry. I mean, certainly not. You wouldn't -- no, there is no representation of patients with acute MI, I'm sorry.

CHAIRMAN PACKER: In that regard I think we can all conceive of studies that can be done in patients with acute MI that would shed light on efficacy and/or safety. There are no data on patients with an acute MI in this data base.

We have discussed that deficiency earlier. How much of a deficiency do you think that is, and how should the absence of that affect either approval or labeling?

DR. KONSTAM: Yes. Again, just give my opinion about it. I'm not that troubled by it. I feel as though the sponsor made a decision to constrain the population in that way. It is a common

judgment.

I agree that there is concern, you know, with the implication, that there is concern that once approved the drug might be used in acute MI, but I think that we could -- the sponsor, you know, in the labeling, would clearly state there is no experience justification or knowledge about the adverse effects that might result.

And I think that my own opinion about it is that to the extent that we are concerned as a committee I think it would probably impact more on what we would like the sponsor to do after approval, than approvability per se.

CHAIRMAN PACKER: And before we just open it for discussion, so that we can just complete the line of reasoning, to what degree is your sense of, I shouldn't say comfort with the absence of acute MI data, but willingness to see that pursued post, as opposed to pre marketing related to the fact that it is a vasodilator would you feel differently if it had a different mechanism of action?

DR. KONSTAM: No, I wouldn't feel

differently.

CHAIRMAN PACKER: General discussion on this. Jay?

DR. COHN: I think that the absence of data in an ischemic population is of some concern because many patients who present this way may have subclinical ischemia that is unrecognized, and it would be reassuring to know that there was no adverse events taking place in patients who are having unstable angina, or acute MI, or having even silent ischemia.

I think we can probably assume, from previous experience, that that is not going to be the case, but it is a deficiency in the package, and would obviously require that that group not be treated.

DR. KONSTAM: Just another comment about the patient population. It strikes me that patients who are hospitalized for worsening failure, who are congested, which is the prerequisite for entry into these protocols, are patients who are to be considered for therapy, aggressive treatment, are always patients who have failed diuretics. At least inadequate

response to aggressive attempts at diuresis.

And I think the population that was entered into this protocol, by design, and I understand the reason for it, this is an incredibly difficult patient population in whom to do a control trial.

But by design these were patients who had not been necessarily aggressively treated with diuretics and had failed, an in fact, it was a prerequisite in the protocol to stop the therapy some hours before the trial was undertaken.

So it seems to me that this is really not the population that those of us around the table would choose to use a drug other than a diuretic until the patient had failed to respond adequately to the diuretic.

And I think that is a deficiency, it may be an unavoidable deficiency, but it raises real concerns about the population who you are going to eventually utilize the drug in.

CHAIRMAN PACKER: Is there any more discussion on patient population? I must say I, for

one Marv, I guess I'm more distressed than you are about the absence of data in patients with acute myocardial infarction.

I think that the risk to benefit relationship may be different in the acute ischemic setting. Now, having said that, it is a little bit hard to calculate that in any reasonably sized trial, because the benefit here may or may not be based on hemodynamic, and therefore harder to quantify relative to any identifiable risk, and how large is the study in acute ischemic settings have to be to identify quantifiable risk.

I would say that, and this perhaps reveals an inappropriate bias, and that is that I guess I'm a little bit more reassured by the fact that it is a vasodilator. I might not be so reassured if it weren't. And I think that is -- I think that that is a bias which is revealed from the Committee's deliberations from a year ago, when we recommended that certain relabeling be pursued for IV positive inotropic drugs, but not for IV vasodilators.

So I think that we may, in fact, be guided

by what we think is the mechanism of action here, but I for one would not like to send this signal to the community that the absence of acute MI data here is acceptable, because I feel that a substantial percentage of patients who come in with acute heart failure have an acute ischemic settings, they are not enrolled in these trials, because they are excluded from these trials.

DR. KONSTAM: Let me just respond to that. I mean, I agree completely that we don't have any safety or comfort measure around the use of this agent in acute MI.

I agree with that wholeheartedly, and that is a considerable issue. I guess, you know, where maybe we differ a little bit, is just our personal response to that in terms of what a sponsor needs to do in developing a drug for acute decompensation of heart failure.

My own bias about it is that if I were very, very confident about the safety and efficacy of a drug for management of acute heart failure, in a program that had excluded acute MIs, I would say I

know nothing about this in acute MIs, now go do a post-marketing study.

But I think that that is really a very subjective decision.

DR. PIÑA: I think your point is well taken, Milton, and it is underscored by the fact that we know that drugs that are not necessarily approved for one thing will be used for that use, regardless of what we say here.

CHAIRMAN PACKER: I mean one of the things is we can recommend to Ray and the division that specific wording be put in that there is no data in patients with acute myocardial infarction, and undoubtedly that should be done, and undoubtedly that will be done, and undoubtedly it won't make any difference, whatsoever.

Yes, we will -- Ray, we wan to you to do this, we want you to make it perfectly clear we have no idea whether what we have just requested you to do, or recommended that you do will be meaningful in clinical practice.

DR. LIPICKY: I understand that, and we

will do as you direct. And do you care about systolic/dystolic dysfunction?

CHAIRMAN PACKER: Is that a global philosophical question, or with respect to --

DR. LIPICKY: No, you don't have to answer that.

CHAIRMAN PACKER: Okay. Cindy?

DR. GRINES: I guess I would also like some additional data in the ischemic heart disease population, but I'm not quite as concerned, because I think we've all been, you know, sort of inundated with ace inhibitors for acute MI, and you know, nitro, etcetera.

I can't imagine that anybody is going to choose a drug like this for a first line agent for acute Mi.

And then the second thing is that, well, maybe they will, but there are so many other proven therapies that reduce mortality.

The other thing is that I think when you get a complicated acute MI patient he is very unlikely to stay in a very small community hospital without a

Swan.

We get a lot of those patients transferred. So I think it is less likely that a family practitioner, somebody who is less experienced will be caring for them.

CHAIRMAN PACKER: Number 3, in patients who, like those studied, what is the dose response relationship, if any, between Nesiritide and decreases in pulmonary capillary wedge pressure. And then go on to answer all three subquestions; how long does this effect last, how does the effect compare to that of convectional therapy, and what are the data to support your conclusions.

DR. KONSTAM: Yes, I think this is a source of some discomfort, because we don't have clear indication from the pivotal trials precisely what is the dose response with regard to wedge pressure of this agent, particularly within 311, there doesn't seem to be any benefit of the .03 dose compared to the .015 dose. In fact, some of the data looked like it goes in the other direction.

And so some of the other trials look like

there is a dose response around that dosing, but it is not quite clear. So I'm left not quite sure of that.

As far as how long does this effect last during continuous administration, we do see up to 24 hours in protocol 311, the wedge pressure effect is there, clearly, although I think that there is some loss of effect at 24 hours, as Dan has pointed out, it is not clear whether that is a pharmacokinetic issue, or pharmacodynamic issue.

How does this affect compared to conventional therapy? I don't think we have any idea about that, because we don't have any comparative hemodynamic data with conventional therapy.

And that is it.

CHAIRMAN PACKER: Three actually does need to be ever addressed, you already citing the data for the first three questions.

Discussion on the effects of the drug on pulmonary wedge pressure, is there agreement or disagreement with Marv's conclusions?

DR. COHN: Let me make a few comments

here. In lieu of my consultants, bypass, let me make a few comments, because I think they are pertinent here.

I'm very sympathetic to this drug for a lot of reasons. And they really go back many years with my -- some of the early studies that we did with atrial peptide.

The virtue of this drug was, at that time, or this group of agents, this peptides, was at that time that they were vasodilator, they were naturietic, and they were neurohormonal inhibiting.

And that is a very attractive profile. Unfortunately despite my sympathy for the concept, the data really have not borne out the original hypothesis, that these drugs would indeed have significant naturietic and diuretic effect in this patient population, that they would significantly inhibit neurohormonal mechanisms which are pretty borderline at best; and that they were potent vasodilators that would be predictable and titratable.

So the weaknesses in the data, I think, reflect the fact that the initial enthusiasm for the

multiple effects of this, physiologic effects of this class of drugs has not been borne out in the patient population that we are using it in.

Now, one of the fascinating things about this drug, it is an endogenous peptide. Now, that is wonderful from the standpoint of safety, but it places potentially a burden on the sponsor, because you are not studying the dose response of a foreign agent, you are studying adding BNP to already existing BNP levels.

And, therefore, the dose response is really the response as you increased the dose of -- the circulating levels of BNP, and in fact, we have no data, that I'm aware of, that gives me any insight as to whether the dose response differs in someone who begins with a BNP level of 50, versus someone who begins with a BNP level of several hundred, you are going to be on a totally different portion of the pharmacokinetic dose response curve.

And I don't see any of those data here. And, in fact, when one looks at the data, there is not a convincing dose response to the infusion rate, and

it would trouble me in terms of deciding how to administer it.

Now, when we give nitroglycerin, or sodium nitroprusside, which are very effective and potent agents, we titrate them very carefully, and we use if we have invasive monitoring, we use the wedge pressure as a goal, and if we have, we don't have invasive monitoring, we use blood pressure as a goal, and we titrate until the blood pressure gets to an unacceptable level, and it is a very comfortable way for physicians to administer a potent vasodilator and achieve the reduction in wedge pressure with safety.

Now, this is a whole different ballgame. We are beginning with a dose which as Dan pointed out, may be close to the top of the dose response curve. We are beginning with the same dose, and people who have a baseline BNP of 50, and those who begin with 700, so they are probably a different kettle of fish, and we don't really know how to deal with that.

And we can't comfortably determine that if are unhappy with the response at .015, that we should then go to .03, because we aren't really sure we are

going to get an added effect. In fact, that has never been the design of the studies, they were done with dose finding, and not with dose titration.

So I think there is some serious limitations in the data base, fascinating as this agent is, which makes it very difficult for me to write a prescription as to how to give the drug, and how to monitor the response, and how to assure safety, and how to choose the patients who should get it, and it just leaves me feeling that we don't know enough about what the drug does to sodium excretion.

I mean, it lowers out aldosterone levels, but we don't know anything about what that may help preserve potassium, because we don't have sodium potassium data, and it is a very difficult group to get it in.

So I recognize the sponsor's problem in trying to quantitate this sort of thing in a very sick population. But these are some of the theoretical benefits. The document suggests that you can get this lowering of wedge pressure without an increase in heart rate, which makes this a very attractive drug.

But nitrates and nitroprusside don't raise heart rate either.

So those vasodilators which are standard therapy are not associated with tachycardia, and not associated with rises in norepinephrine, so that we don't really have a clear distinction between this drug and other therapies that can be utilized.

And we have a bit of a problem in that the traditional way to administer these drugs with titration up to desirable effect does not pertain here, and we are now facing a whole different way of administering a vasodilator drug without the ability to titrate.

So these are some of my concerns with what otherwise is a very attractive agents.

CHAIRMAN PACKER: Let me see if we can get some clarification. Ray, I'm going to ask you to help us on this.

There has been a distinction drawn in the past in the evaluation of drugs for heart failure, between how IV drugs are thought about, and how oral drugs are thought about. It is not uncommon in -- and

there has been an evolution of thought in the past decade, that much of oral therapy has been driven by an effect on clinical status, or clinical events.

And although there may or may not be dose response data for oral, there is generally a concept of titration to target dose, which dominates the oral field, largely because the large scale clinical trials looking at clinical events did that.

The thinking that has dominated IV drug therapy for heart failure, and I think you made this point a year ago, was that if one could show a dose response relationship for hemodynamics then one could write labeling for a drug because knowing that allowed someone to tell physicians how to use a drug in accordance to the way they would normally use the drug.

Now, in all other case of drugs for IV use for heart failure, and maybe for many other conditions as well, cardiovascular conditions, there has been a relationship between dose and -- there is always a relationship between dose and response, but the doses explored have included a range of doses which have

exhibited a range of effects.

On the package in front of us today suggest that there is one or maybe two doses that have a pharmacological action which is deemed desirable, not necessarily a dose response, because they may have been at the flat part of the dose response relationship, and clearly no dose response relationship for symptoms or whatever, there are no clinical events to analyze that are meaningful.

So the philosophy here is more like an oral than an IV agent, even though the administration of this drug is IV. And if -- but physicians still practice medicine in a dose response world, which I think is what Jay is referring to.

The previous guidance was dose response.

DR. LIPICKY: You are asking me a question?

CHAIRMAN PACKER: Yes.

DR. LIPICKY: Let me respond. Everything you said is correct, okay? But it is going to take a little while for me to respond, and it should take me very long to respond, because the concepts involved

are very difficult.

Probably the place to start is with dose response. I disagree that there is no dose response in this data. Clearly the two doses studied changed things compared to placebo, and the stuff was there before. So you actually have three data points that you can look at, all right?

And the dose response is somewhere between what the basal level was, and what these two doses produced.

So, indeed, the interpretation that you may be near the top is correct, if your model says that there is a continuous relationship between plasma concentration and effect, with some lag.

And so the EC50 is somewhere down below either of the doses that were shown in these trials.

We will go back and look at the other trials to see if we can reconstruct some kind of conglomerate dose response. That was an error, I think, on our part for not doing that before, because I would function from the vantage point that there is a continuous dose response relationship, and this just

represents one end, with the limit being hypotension.

And we ask people to get to the limit and so then the idea was, let's back off from that limit a little bit.

Now, so first there is a dose response here. Second, the notion that in chronic heart failure one should titrate to maximum dose, is an artifact of the number of dollars people are willing to invest in a chronic heart failure program.

They are not willing to invest finding what happens at each dose. But will invest in saying let's find the biggest dose we can use, and get away with, and compare that to placebo. That is not science, it is not anything else, it is just strict dollars.

What people think, and in fact anoximone, for example, is being currently worked up at a very much lower dose than at any of the doses in other trials, with the notion being that big doses of inotropes kill you, and the doses that you need are much smaller, and they will help.

So there is a real defect in this titrated

business. The next part of the same business dose response was that if you went around the table and asked people if one had really characterized the dose response for any one drug. I don't care what drug it is, or what condition you want to use it in.

And you said, what dose would you start with? Some people would say, probably somewhere around the ED10 or ED20, and then titrate from there.

Some would say, I wouldn't start any lower than ED50, why would I want less than half the people I treat to have some response? Others would say, I use the ED90, first dose.

And some of those considerations would depend in part on what the adverse effects were, and how the adverse effects related as a function of dose.

So then the next concept is that when you vary doses by a factor of two, I'm supposed anybody ever finds a difference in anything, okay? It is almost certainly log plasma concentration, for any effector, and you vary the dose by a factor of two, your N has to really be large to find a difference in biological response.

So the fact that people don't find differences in biological response with factors never surprises me.

Now, so I think everything you've said is right, it just, from my vantage point, this drug has a dose response relationship, it has been fairly reasonably described. The trouble is it hasn't studied a dose in empirical trials that will allow one to say, I know what dose is the smallest dose I would use. Pretty well characterized what the largest dose would be.

CHAIRMAN PACKER: Dan actually emphasized that point before.

DR. LIPICKY: I understand. Then the other part of the thing you were talking about, and I'm not sure I'm really being responsive, is that if there was an acute heart failure and a chronic heart failure program for any drug, the chronic heart failure program would be the thing that would probably, in some conceptual sense, identify that this is a useful agent, that would establish efficacy.

Then for acute heart failure, it is very

easy for me to say all you have to do is find what dose you would use, and find that it is -- it does consonant things, and that it affects hemodynamics reasonably.

The big problem is when you have only an IV acute heart failure drug, then you don't have the long term chronic stuff to help you.

And then the IV has to be -- has to have a little more to carry itself, because it doesn't have this other part to help establish its efficacy.

Now, I don't know if I really responded the way you wanted me to, or if I got at any of the points you wanted to --

CHAIRMAN PACKER: What it allows us to do, I guess, tie Jay's point together with Dan's point, and just ask the Committee how concerned are they that a dose that is lower than the plateau dose that may or may not have been identified in this trial, that has not been identified here, how and the question is, is the lack of such identification meaningful in this NDA, and because it is frequently done.

Jay, I think in paraphrasing what you

said, that usually is something that facilitates the use of a drug in an IV acute setting. We don't have that kind of dose here, it is more give this infusion, and pretty much you will get a lot of what you would expect with the drug.

How does this Committee think that the lack of such identification is a limitation to the present data base? I would like to hear more discussion about that.

DR. COHN: Let me just ask one question, first. Do we have BNP data so that one could actually analyze whether that impacts upon the dose response effect?

DR. GROSSBAR: As I understand it, the plasma concentrations were derived by subtracting the baseline BNP. So when you see the plasma concentration curves, they reflect the BNP level minus the baseline BNP.

DR. COHN: Baseline values, then, on each patient?

DR. GROSSBAR: On everyone.

DR. COHN: On everyone?

DR. GROSSBAR: On everyone.

DR. COHN: Have you done any analysis to see whether there was an impact upon the response based upon what the baseline levels were? It seems to me it is a key issue here, because where you are dealing with an endogenous peptide --

DR. GROSSBAR: I'm not so sure I will concede it is a key issue, because that would make the predicate for the infusion of the drug the use of a diagnostic test that is not available.

DR. COHN: It is a key issue in us for understanding the drug.

DR. GROSSBAR: So we will tell you what we know.

DR. SAMBELL: I want to say, first of all, that we did actually do a concentration effect analysis after the NDA was submitted. We felt that it was an important issue, and it would help to clarify some things.

And maybe more so for those that believe in modeling, which I do to a certain degree.

And what that modeling has shown is that

there is a graded concentration effect relationship in the range of concentrations seen with at least the single dose studies, and that is the data that we used for the modeling, because it gives a much broader range of concentrations.

There is a slight lag between the effect relative to the concentration, and my feeling from that analysis, and what is coming out of that, is that we are actually operating in more of the linear region of the dose or concentration effect, relationship if you are looking at a saturable model altogether.

And this finding that the .015 and the .03 do not differ significantly in this one study, I think is an aberration. And I would not be misled by that. I think you need to look at the whole picture.

The other thing that we did look at is whether there was a relationship between endogenous concentrations and the, if you will, the D50, or C50 in the concentration effect relationship.

And there didn't seem to be any apparent relationship between that baseline and the response,

although given that it is a significant issue with something that we can go back and look at further.

DR. COHN: Two real quick things. So this was with respect to wedge pressure?

DR. SAMBELL: This is with respect to pulmonary capillary wedge pressure.

DR. COHN: And the actual concentrations of the peptide on treatment were orders of magnitude greater than baseline, or two-fold?

DR. SAMBELL: The actual data that was used in the analysis was from study 309, so that was as much as 10 micrograms per kilogram given as a single bolus in actual multiple bolus.

DR. COHN: So plasma concentrations on treatment were orders of 2, 1, 2, 3?

DR. SAMBELL: Maybe 10 or more.

DR. COHN: Ten orders of magnitude greater than baseline?

DR. SAMBELL: Yes. I can give you those exact values. Tenfold.

DR. COHN: Tenfold?

DR. SAMBELL: Right.

DR. COHN: So one order of magnitude.

DR. SAMBELL: Well, at least, it could be more than that.

CHAIRMAN PACKER: We should clarify one thing. I don't think anyone here is saying there isn't a relationship between dose and effect. I think that what the only thing that we are struggling with here is the pragmatic issue as to whether there is a relationship between dose effect within the recommended range.

If one goes to .06 or higher doses, one is going to get more of an effect, but there will be more hypotension, the sponsor is justifiably uncomfortable with that.

And for reasons that Ray mentioned, there is a relationship between dose and effect here. But that is to be distinguished from, I think, the issue that Jay mentioned, which is in the recommended range one is more likely than not to give, in most cases, single dose of the drug, with the expectation that there will be some predictable effects on hemodynamics and perhaps symptoms without the traditional concept

of significant up and down titrations.

DR. LIPICKY: But it is a bit more of a problem since basically the Committee was discussing the business of what would you do if you didn't have a wedge pressure, said I don't know what to look at to tell whether people are getting better or not.

And so then you are sort of stuck with having some empirical information at hand that tells you what dose would be reasonable at the smallest dose, even though I can't suppose that I could have the smallest dose that has been studied, and would still have an effect, but that is probably my imagination.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: I just want to actually concur that my best explanation for the specific observation with regard to the .015 and .03 doses in 311 is probably, my most likely explanation would be that it is an aberration related to the .03 group, as opposed to Dan's concern that we are actually at the top of the dose curve, and the reason for my saying that is, first of all, the .06 dose within that study

does have a higher wedge pressure.

And, furthermore, there is a dose response relationship within 325. So I think, at least my level of concern around this really relates to just how much, you know, hard data. What do we really know from 311 as opposed to what is the most likely dose response relationship here.

CHAIRMAN PACKER: Fine, then let's just -- I think that there is general consensus amongst the Committee on 3b, which is, there is no direct comparison data on wedge pressure.

So let's just get a sense from the Committee, we can go around very, very quickly. Are you or are you not concerned that the sponsor has identified a dose which gives, in effect, significantly less than their starting dose?

In other words, how concerned are you that their initial recommended dose is close to their plateau dose in terms of the general use of the drug? It could be you are not concerned at all, it could be that you are concerned, and I think that that would epitomize some of the issues that Jay brought in, and

Marv, than has now commented on.

Because clearly, if you are not concerned, then this issue goes away. So let's start. Joann, how concerned are you that this is -- that there isn't a dose lower than the plateau dose in order to initiate therapy?

DR. LINDENFELD: Well, I am a little bit concerned, but I'm not terribly concerned. On the other hand I sort of like the idea that side effects are relatively low, and this is a dose to start on, and you get a definite effect, and it may decrease hospitalization, there is not multiple assessments.

So I'm a little bit concerned, but not terribly concerned about it.

CHAIRMAN PACKER: Lem?

DR. MOYE: It is not my greatest concern, but I am concerned.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I am somewhat concerned, not strongly concerned.

CHAIRMAN PACKER: Marv?

DR. KONSTAM: Well, I'm somewhat

concerned. I think that there are a number of questions about this drug, and I think we have just one more, that in one pivotal hemodynamic trial we don't clearly see that differential that we like.

So I think I'm somewhat concerned.

CHAIRMAN PACKER: Tom?

DR. GRABOYS: Well, I'm concerned because I think in order for practitioners to understand how to use this drug they are going to have to have some sense of dosing. And once it is in the community, these selected adverse events, or side effects, are quite significant.

You are looking at 40 percent of selected adverse reaction as compared to about 20 percent for a control. So I think those numbers will probably increase. So I think that is of concern.

CHAIRMAN PACKER: Dan?

DR. RODEN: I think it is a concern, I don't think it is a necessarily a fatal or limiting concern. I think that Ray's suggestion that the Agency go back and look at the plasma concentration response data as they are being generated, and as we

don't see them right now would be a reasonable way of figuring out whether a lower dose might be something to think about as the package insert is written, without data.

CHAIRMAN PACKER: Cindy?

DR. GRINES: Yes, I think it is of minimal concern to me.

CHAIRMAN PACKER: I'll just say I don't think it is a concern at all, only because if I have a drug that does what I -- a dose that does what I want it to do, and it is well tolerated, I don't mind that conceptual model.

DR. LIPICKY: You are all ED90 people?

CHAIRMAN PACKER: Yes, ED90 people. I never though of myself as an ED90 person before. But we are not all ED90 people, some of us are ED50 people.

DR. LIPICKY: There were some exceptions.

CHAIRMAN PACKER: How concerned, and Marv mentioned this before, the data for 24 hours, there may or may not be any attenuation at 24 hours, is literally impossible to tell.

The -- maybe we should ask, is the sponsor proposing use only for 24 hours? Because that is not clear in the proposed labeling.

DR. GROSSBAR: In the question, the final question Dr. Lipicky asked, define acute treatment as less than 24 hours. The sponsor was less specific, and hoped to gain labeling similar to that which is used for other products in this indication, which is not terribly specific about duration of therapy.

CHAIRMAN PACKER: Okay. Taking -- let's assume for a moment, because otherwise it makes discussion unbelievably complicated, the labeling, as one of the latter questions indicates, question number 12 indicates to be specific for 24 hours.

How concerned are you about the potential for attenuation? And let me just suggest, to facilitate discussion, you may be not concerned at all, given the data, if in fact the drug would be used for 24 hours because you've got data to 24 hours.

You may say that you don't know much beyond 24 hours, and you wouldn't want to suggest that there are data, or that the drug would be recommended

for use beyond 24 hours. That would be a very empiric approach.

The question is, does the Committee agree with that empiric approach? Marv?

DR. KONSTAM: No matter what the labeling is, this drug, if approved, will be used far longer than 24 hours.

CHAIRMAN PACKER: That doesn't matter, because it is like the acute MIs discussion. The question is, do you want the labeling to reflect that?

DR. KONSTAM: I think it is a little -- not perfectly analogous with acute MI discussion, but the --

CHAIRMAN PACKER: Do you want the labeling to reflect that?

DR. LIPICKY: You are asking whether people are comfortable that the effects last for 24 hours?

CHAIRMAN PACKER: We are addressing the question about attenuation, does this effect last during continuing administration.

DR. LIPICKY: And you chose to limit it to

the --

CHAIRMAN PACKER: One needs to define what that time frame is in order to answer the question.

DR. LIPICKY: Right.

CHAIRMAN PACKER: We can't define that time frame beyond 24 hours. And there is a -- if there is evidence for attenuation before it may become more marked after.

DR. LIPICKY: Right. But the question you asked Marvin was for 24 hours will the effect be --

CHAIRMAN PACKER: That is right.

DR. LIPICKY: And that is the only question you have to answer now.

DR. KONSTAM: I'm sorry, what is my question?

CHAIRMAN PACKER: Is there an effect for 24 hours?

DR. LIPICKY: Will the effect you get last for 24 hours.

DR. KONSTAM: Yes. Well, we have an effect for 24 hours, there may be some attenuation.

CHAIRMAN PACKER: Does anyone disagree?

(No response.)

CHAIRMAN PACKER: Let's go to question 4, it is exactly the same principle, the difference here is the hemodynamic variable is different, and let me just, for the sake of time and clarity, say that this can apply to all other hemodynamic variables that you think are important, other than just cardiac output.

Marv?

DR. KONSTAM: Yes, I think the answers are identical for those for the wedge pressure.

CHAIRMAN PACKER: And you are not concerned that statistical significance was not reached on these other variables in the only study that looked at them at 24 hours?

DR. KONSTAM: Which parameters are you talking about?

CHAIRMAN PACKER: Cardiac output, right atrial pressure, systemic vas resistant, all of them were no longer statistically significant at 24 hours in the only study that looked at it.

You may not be worried about it, I just want to know whether --

DR. KONSTAM: Well, I would have to go -- my general sense, having looked at the data.

DR. LIPICKY: He just gave you a new fact.

DR. KONSTAM: Yes, I missed that fact, to tell you the truth, about the loss of statistical significance at 24 hours.

DR. LIPICKY: You just knocked something new in, though.

CHAIRMAN PACKER: No, that was mentioned by the sponsor in their presentation.

DR. GRINES: It is slide 21, although the relative effect looks pretty similar, there is no longer statistically significant, and it is due to variation.

CHAIRMAN PACKER: Yes, the P values actually are in the document, that in study 311 there is an effect compared with placebo at pulmonary wedge pressure at 24 hours, but not for the other hemodynamic variables.

As Cindy has emphasized, the dose response relationship is still there if, you know, in other words relationship between -- I hate to use that

because we just discussed -- the relationship amongst doses is still there. But none of those effects are statistically significant.

I believe I'm saying, correctly, for any variables other than wedge pressure. I don't know if that is a true statement.

DR. KONSTAM: Let me just -- I'm not sure whether the P values at 24 hours are really the critical question, quite frankly.

I think, and maybe we will have to call on Lem on this, but let me just give you a sense of the answer to this question. I think the drug has a beneficial effect on all of these hemodynamic parameters. I think that is my conclusion from looking at all of the data.

And I think that my sense of it, looking at all of the data, is that there is a continued effect on 24 hours, regardless of what the particular P value happens to be at that point, that is my opinion, looking at all the data.

I do think there is evidence for some loss of effect. So I guess my answer is, now that you

pointed out to me, I'm not overly concerned, per se, about the fact that P values disappear at 24 hours.

CHAIRMAN PACKER: Okay. Any general discussion before we go around and just get the consensus?

(No response.)

CHAIRMAN PACKER: Well, why don't we start the same way. Joann, basically do you agree or disagree? The issues here don't relate to minimum dose, they more relate to more persistence of the effect.

DR. LINDENFELD: I think there is persistence of effect.

CHAIRMAN PACKER: Lem?

DR. MOYE: It is my pleasure to agree with Marv.

CHAIRMAN PACKER: To?

DR. MOYE: To agree with Marv.

CHAIRMAN PACKER: He agrees with you?

DR. RODEN: I'm shocked.

DR. MOYE: If you want me to talk for a couple of minutes about P values here?

(General laughter.)

DR. MOYE: I have a few brief remarks here.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I agree.

CHAIRMAN PACKER: Tom?

DR. GRABOYS: I agree. I agree that the effect is preserved, but there is no dose response in that effect.

CHAIRMAN PACKER: Okay. Cindy?

DR. GRINES: I agree.

CHAIRMAN PACKER: I agree, as well. It is exactly the same situation with respect to symptoms. The issues are similar, the -- it is three separate questions. The only question that is -- forget about 5c, the questions are one, is there an effect on symptoms; two, is there a relationship between effect and dose? Three, how long does the effect last? And four, how does it compare to conventional therapy.

Marv?

DR. KONSTAM: I actually think that some of the issues here are different. And so let me just

preface the answer here by saying my own view about this, as I said earlier, is that I'm looking here for confirmation that the effect on wedge is clinically relevant, rather than looking at it as a -- you know, as a necessary isolated finding for approvability's sake, but rather confirmation of the clinical relevance to the wedge pressure reductions.

So let me just start with that. I think that there are a lot of problems with the symptom data, and we've really dwelled on those. I think they could be done better in the future, but now we are left with this data set.

Presented with this data set, I do believe, looking at it through the issues, there still is a demonstrable effect on symptomatology. And, actually there appears, to the extent that we accept that, there actually appears to be a dose response in study 325. So I guess that is one set of answers.

In terms of assuming that that is correct, how long it lasts, that becomes a little confusing. So we don't have a placebo control at 24 hours. We have, in study 325, after six hours the drug therapy

is opened up, and so we have it compared to what is called conventional care.

And there we do not have any significant differences across, from between standard care and drugs, an active drug at 24 hours, although the apparent improvement that we saw in 6 hours, in the Nesiritide groups appears to be sustained.

So you can interpret that in a few different ways. You can say, well I think that we actually have made patients better, and they probably are still better at 24 hours.

Or you can say, well you know, this drug really didn't do any better than if I didn't have it. And actually there is a trend at 24 hours toward it being a little bit worse than standard care, but that may be related to a lag in getting certain other kinds of therapies going.

So we are left a little bit unsure about what -- I mean, I think the 24 hour data are there, but I think that they are open for those sorts of interpretation.

CHAIRMAN PACKER: Marv, just taking off on

what you said there, I guess there are three ways of looking at the symptom data.

One, they are terribly flawed, and one can't interpret anything. Two is that they are sufficiently flawed that one can gain comfort about the meaningful of the hemodynamics, but not sufficiently comfortable to provide a claim.

Because the sponsor is asking for a claim.

DR. KONSTAM: Related to symptom improvement?

CHAIRMAN PACKER: Yes. It says, proposed indication statement, sorry to keep on referring to this, it also causes rapid symptomatic improvement.

And the third possibility is to say both your comfort level with hemodynamics and the claim is acceptable.

So I'm sure there are all sorts of levels of comfort in between those two, but just to make it very, very straightforward, one is a claim, the sponsor would like that claim; two, it is good enough to give one comfort about hemodynamics but not good enough for a claim; and three, it is not good enough

for either.

And I think that it will allow us to sharpen our thinking very well if we can define the level of comfort and if we can do that, then a lot of things fall into place. Is that fair?

DR. KONSTAM: Yes, I think that is good. And I would say, somewhere around level 2 is where I'm at.

CHAIRMAN PACKER: Level two is comfort that the hemodynamics are meaningful, but not enough for a claim?

DR. KONSTAM: Right, but let me, since this is a new question for me, let me ponder it for a second. You know, I think that is right, based on everything that we said.

However, I would just make a distinction. Based on what I've seen I wouldn't mind, assuming the drug were approved, seeing that reported in the packet insert, that these observations were found as opposed to the claim per se.

CHAIRMAN PACKER: I guess that is a sort of -- it is subgroup of A?

DR. KONSTAM: Right.

CHAIRMAN PACKER: Okay, fine.

DR. LIPICKY: Those one, twos, and threes were real numbers, not integer numbers.

DR. KONSTAM: Yes, 2.2.

CHAIRMAN PACKER: Okay, does everyone understand the options? The options are: One, it is good enough for a claim; Two, it is good enough for a comfort level for hemodynamics; Three, it is not good for either. And Two-two comfort level for hemodynamics.

DR. GRABOYS: A good comfort level, not a claim.

DR. RODEN: Two.

CHAIRMAN PACKER: Cindy?

DR. GRINES: Repeat the question?

CHAIRMAN PACKER: Yes. Are the data on symptoms in your view good enough for a claim, because that is what the sponsor is asking for; good enough to give you comfort that the hemodynamic changes are clinically -- maybe clinically meaningful, or three, are they good enough for a neither?

DR. GRINES: I think it is good nough for a claim.

CHAIRMAN PACKER: Joann?

DR. LINDENFELD: I think 2.

CHAIRMAN PACKER: Lem?

DR. MOYE: Three.

DR. PIÑA: Two.

CHAIRMAN PACKER: I would vote three, actually. So that, in fact, it is one 1, two 3s, and the rest 2s, the 2 is the majority. Cindy was one.

DR. LIPICKY: One was it was no good for nothing?

CHAIRMAN PACKER: No one is good enough for a claim.

DR. LIPICKY: Three is it was not good for nothing?

CHAIRMAN PACKER: Right. Well, we didn't say good enough for nothing, we said neither.

DR. LIPICKY: Right. Are you sure you have that, Joan?

SECRETARY STANDAERT: Yes.

DR. LIPICKY: Okay.

CHAIRMAN PACKER: The Committee, the consensus of the Committee is that it is good enough for a comfort level that the hemodynamics are meaningful, clinically meaningful. That is the consensus for you.

And in terms of persistence effect, and comparability of the effect, right now the data, as Marv has summarized it, the data are placebo controlled. Actually, we don't necessarily have to tackle all of that, since we now have answered two, is that right?

That solved that problem. Okay, good.

Six, at the beginning of the drug infusion what is the time course of the onset of effect, what is the time course of the offset of effect? Are the time courses similar for the beneficial and adverse effects? Are the data as to the time course that changes the effect after changes in the infusion rate.

Marv?

DR. KONSTAM: Yes. I think the time to, I think it is measured in hours. I'm looking at a graph on page 47 of the medical review, which

basically shows that in -- that the maximum effect, maximum wedge pressure effect is showing up in the three to four hour range, following initiation of infusion.

And that the time to offset similarly, from what I can see, is hours, maybe a couple of hours to the elimination of the effect.

I think that we really -- this is a concern, that we don't really know whether these time courses are similar for the beneficial or adverse effects.

I mean, I guess the adverse effect for which this makes some sense is the hypotension. And I've raised that concern, that we don't have -- I don't have a clear sense of what happens to blood pressure after we stop it.

I get the sense, from the data that was mentioned that, again, it is of the order of a couple of hours before the hypotensive effect is off.

So we don't have any data here about the time course of the change of effect after change in infusion rate.

CHAIRMAN PACKER: So the onset of the effect is within hours the time courses of whether or not there is a tracking of the beneficial and adverse effects is unclear but likely?

DR. KONSTAM: Okay, unclear but likely.

CHAIRMAN PACKER: Unclear but likely is, I think, an accurate description of the data, no? Right?

DR. RODEN: That is for blood pressure?

CHAIRMAN PACKER: Yes.

DR. RODEN: But for creatinine --

CHAIRMAN PACKER: Right, for creatinine we don't know.

I get the impression that a lot of this is focused on adverse hemodynamic as opposed to adverse laboratory, because adverse laboratory doesn't really have a time constant. Isn't that right?

DR. LIPICKY: Well, it was mainly for the continuous things that are measured frequently, because in fact the laboratory was measured like once a day, or once every other day, and it is hard to describe its time constants.

CHAIRMAN PACKER: Anyway, I think Marvin has basically described it. Are there any disagreements? Dan?

DR. RODEN: I'm still troubled and struck by the fact that the wedge pressure changes occur over three to four hours, but the cardiac index changes in both the pivotal studies occur at the first time point.

And so I come back to the issue of boluses versus infusions, of multiple pharmacologic effects. So I would sort of modify my answers a little bit, but otherwise I agree with Marv.

CHAIRMAN PACKER: Okay. Let's move on to 7. What is known about the co-administration of the drug with other vasodilators? Marv.

DR. KONSTAM: Well, really very little. I think the only information we have at all about this is from study 325, after the six hour timepoint when the patients were opened to receive whatever therapy.

And we have some descriptions of what happened to that population, but really nothing systematic. There were a variety of different agents

used, and it really isn't, it isn't enough to know what effect this agent has on top of -- on top of other such agents.

CHAIRMAN PACKER: Jay?

DR. COHN: We did see some data on the co-administration of ace inhibitors, which was a little bit disturbing. And of course ace inhibitors stimulate kinanes and increase nitric oxide levels, and stimulate cyclic G, so there may be some dual mechanism here that we have to pay attention to.

I guess the same thing would be true with a nitrate, and there is a lot of data with patients who are taking oral nitrates. And, once again, I don't know whether this drug will have a greater effect in patients on nitrates, or with co-administration of nitroglycerin, and I think that is something that we certainly should know.

I guess to go beyond the vasodilator I think there is a concern about what the drug does to co-administration of a loop diuretic. Do we have any data to tell us whether there is any interference with, or augmentation of, the loop diuretic effect.

These are the sorts of things that would have to be done not in phase III studies, but really back in phase II, to really do some drug/drug interaction studies. Maybe they have been done. But I feel, on the basis of the data that I've looked at, that I'm a little insecure about how this vasodilator mechanism interacts with diuretics and with other vasodilators and whether that should be an important consideration.

DR. KONSTAM: Can I just follow up on that? I mean, that is a very good point, and we saw something that Ray's concern, it is going to come back at us when we are talking about adverse effects.

But as Jay points out we do have some data about concomitant administration of ace inhibitors, and it is concerning data because, in fact, the incidence of adverse hypotension was highest in the group with the ace inhibitors, and there was a chunk of patients not on ace inhibitors.

So, in fact, that particular adverse effect may be more prevalent in a population more uniformly treated with ace inhibitors.

DR. GROSSBAR: We actually did a specific study similar to what Dr. Cohn was suggesting with ace inhibitors in phase II, which compared the interaction, specifically of BNP with ace inhibitors, because there had been a pre-clinical study suggesting that ace inhibitors inhibited metabolic clearance of BNP that was a factor in it.

We went to a lot of effort, actually, to replicate that and proved that that is not the case. And when we did the interaction study in phase II, and it was a substantial one, we found absolutely no interaction between BNP and ace inhibitors given as a bolus, I want to qualify that, we used different bolus doses of BNP, looked at ace inhibitors, plasma concentrations, and other side effects.

The reason we didn't make much of that in the presentation is because we recognized that someone could likely come back and say that a narrow clinical pharmacology study like that doesn't really represent what happens when patients are running amok coming into the hospital.

So in a sense I would challenge that you

could go back and do an interaction study with a loop diuretic. You might be able to show some interesting effect on renal function one way or another.

But you would still, in the end, be left with the clinical results that we presented in the large trials, where there was a lot of diuretic use.

DR. COHN: How do you relate that experience with the ace inhibitor with the apparent dramatic efficacy of Nep base inhibitors, which should really combine the effects of a peptide --

DR. GROSSBAR: Are they approved therapies?

DR. COHN: No, but they, you know, there are some --

DR. GROSSBAR: Well, we have to wait until the FDA has had a chance to adequately review that data.

DR. COHN: Okay, but I'm just asking you your opinion. I mean, those two drugs seem to be interactive, at least from published data.

DR. GROSSBAR: I can only report what we did and what we saw.

DR. PIÑA: I am sorry, was that your study 310?

DR. GROSSBAR: 310 and 309. 309 was done without ace inhibitors, and 309 was --

DR. PIÑA: And an --

DR. GROSSBAR: Right. Some people got, you know, but generally it was an aliquot.

CHAIRMAN PACKER: Ray are you happy with the discussion that is taking place on question 7, because clearly you are looking for specific opinions and guidance from the committee here.

Are you satisfied, can we go on to 8?

DR. LIPICKY: You may go on to 8, but I must admit that I don't know what to do with your discussion. I have listened to it, but it isn't clear to me exactly what action to take as a consequence of it.

CHAIRMAN PACKER: Dr. Karkowsky?

DR. KARKOWSKY: The question I had more was there is two ways to put two things together, one to start with this drug, and add something to it, which as you have a little experience in this data

base.

The other thing is to put this drug onto something else. If you are titrating somebody and get an optimum dose of a good drug, let's say a vasodilator or an inotrope, and then you have this drug which is not easily titratable, what would be your outcome, how would you say to use it?

CHAIRMAN PACKER: Okay, I got it. So the question that might -- another way of formulating the question, because the question in 7 was how; and maybe what we should do is have more of a definitive way of phrasing this question.

What should the labeling of this drug say, if any, about whether this drug should be used alone or in combination with other IV drugs for the treatment of heart failure? Drugs with vasodilator -- doesn't even have to be IV, it could be oral drugs as vasodilators.

DR. LIPICKY: Well, other oral drugs were used in combination with, in the trials.

CHAIRMAN PACKER: Yes, right, so the question --

DR. LIPICKY: And the --

CHAIRMAN PACKER: So you want the question to be IV?

DR. LIPICKY: I hear people's reservations with respect to how much specific information there is, and whether things can get dissected out. And, in fact, we didn't see a lot about whether responses were different in people with different drugs on board.

And my problem is I don't know what to do with that, except note it. And I don't know that one would want to translate that into specifying some action that others should take on the basis of that deficiency, if in fact you should ignore that deficiency and recommend approval.

DR. GRABOYS: How can you say anything but that experience is limited with concomitant use of --

DR. LIPICKY: Well, that is not saying anything.

DR. GRABOYS: -- and that is what you have -- that has to be commented on.

DR. LIPICKY: But that is easy to say, I heard the discussion that it is easy to say. But that

doesn't say anything, that is like saying, drive carefully.

DR. GRABOYS: Well, you put signs up that says drive carefully.

DR. PIÑA: That is good advice, though.

DR. LIPICKY: It is good advice, but it doesn't say anything.

DR. GRABOYS: Why is this complicated?

CHAIRMAN PACKER: Ray, just picking up on what Tom has said, is there a problem with saying drive carefully if you --

DR. LIPICKY: No.

CHAIRMAN PACKER: -- don't know any better?

DR. LIPICKY: No, I'm happy to do that, but I think if you keep going you will want me to say more.

DR. COHN: I think the message that you've gotten, Ray, is that there is a deficiency in the data base, and the question as to whether that deficiency in the data base should influence the approval process would relate to many other things in the data base

that may be so powerful that you are willing to exclude that.

On the other hand, if the rest of the data base wasn't very powerful, you might find that this deficiency was an overwhelming fatal flaw.

DR. LIPICKY: And that is correct, and that is why there is an order to the questions, and approval will come down below where all of these things you ought to be noting in your head.

CHAIRMAN PACKER: But I don't get the sense that anyone in this room would think that if a patient was already on an IV vasodilator, I hope I'm saying this correctly.

That the IV vasodilator should be withdrawn when treatment with this drug is initiated. I don't think I'm hearing anyone say that. What should a physician do?

I didn't think anyone would say that, but now looking around the room I don't know what people are thinking.

DR. RODEN: Or lasix, worse yet.

DR. GRINES: Well, at least there is data

on administration of diuretics during the treatment period. But I'm not sure that there was any IV vasodilators given.

CHAIRMAN PACKER: Well, let me see if I understand. Let me make sure. If someone is on IV nitroglycerin, or you can make -- substitute any drug, someone is on something, what -- I hope -- well, let me try to phrase this in a more detailed fashion.

What guidance should be presented tot he practicing physician as to what people should do with concomitant therapy, be it oral or IV, when this drug is administered.

And that is the two-tailed generic question. I didn't think I heard anyone, but Abe's question is right to the point. I didn't think I heard anyone say that they thought that some drugs should be withdrawn before this drug is administered, but maybe that is -- maybe I'm being presumptuous here.

So let me see if I can get a clarification. Would someone help to clarify what the Committee's position is on concomitant therapy, and

what should be either done with this drug, or done with a concomitant therapy?

Because Doctor Karkowsky's point is, gee, there wasn't a whole lot of concomitant therapy, normally one would adjust the dose if someone was hyper responsive, but here there is -- we don't have a whole lot of experience with a variety of doses. Ray has to write labeling.

What can we do? We'll go. Marv and Ileana.

DR. KONSTAM: Well, I'm not sure, but I think one could make a case for making concomitant use of other intravenous vasodilators contraindicated. And let's see why I would say that.

Well, first of all, there is no data to support the safety of concomitant use. The safety concerns that we have about this agent, a part of that relates to the hypotensive potential of the agent.

We have said that the rate of offset of vasodilator effect, or hypotensive effect of this agent is not immediate. And let's couple that with asking ourselves the question, what is the physiologic

rationale for combining this agent with other intravenous vasodilator agents.

So I'm sort of working up to it, but I think you could take that and make a case to say other IV vasodilator agents at this point should be contraindicated, concomitantly with this agent.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I think you have to say what was done here. There were other agents, were withdrawn prior to the initiation of this drug. And what happens with the two together is uncertain.

Now, I also think that you can go on and say that in 326 a whole series of patients were on other concomitant medications, so that -- but that is on the long term effect. But at the acute administration the patients had been taken off other drugs for a certain number of hours.

So that if you have to get a decay of blood level it is gone. So I would assume that whatever was hanging around was gone.

CHAIRMAN PACKER: I hear what everyone is saying. I'm a little bit surprised. I guess this may

be a side effect of living in an ED90 universe.

DR. LIPICKY: Yes, because no one would have any concern if you start at the ED10.

CHAIRMAN PACKER: Right, there would be -- if we lived in an ED10 universe, then none of these issues would exist. But because we live in the ED90 universe they do.

DR. LIPICKY: You have a problem.

CHAIRMAN PACKER: There is a price to be paid for living in an ED90 universe.

Let me just make sure that I understand. Would it be the Committee view that this drug should not be given, that the labeling should, in fact, make clear that this drug should not be given together with other IV vasodilators or other drugs with vasodilator IV vasodilator properties?

I'm just trying to -- in other words, should the package insert reflect what was done in the clinical trials in terms of the withdrawal of the drug? Tom?

DR. GRABOYS: Yes. I mean, you've articulated it very well.

DR. RODEN: I agree. I mean the concern is the hypotension, and any additional IV inotrope, or IV therapy would I think exacerbate that, and there is no data, so I think the package insert should say, should perhaps go so far as to say until other data are available. It is contraindicated, which is a little

different from saying not do it.

CHAIRMAN PACKER: Joann?

DR. LINDENFELD: I agree. At least IV vasodilator I think should be strongly discouraged, if not contraindicated.

CHAIRMAN PACKER: And I guess I imagine that must apply to ace inhibitors, since they have big time vasodilator properties. Lem?

DR. MOYE: Their use should be discouraged.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I agree, as stated my point.

CHAIRMAN PACKER: And Marv, I think you said that? Okay. I'm trying to figure out a way of voting that shouldn't be discouraged, but I can't

rationalize it, so I guess I will agree with the Committee.

Is that clear for seven, now?

DR. LIPICKY: Yes.

CHAIRMAN PACKER: We are saying -- we are not saying drive carefully, we are saying don't drive.

DR. LIPICKY: Yes. No, you are being very explicit about how to drive carefully. Marvin has a problem.

DR. KARKOWSKY: How do you know this isn't the same thing for inotropes? I mean, the mechanisms may not --

DR. LIPICKY: He is worried about hypotension, and Milrinone was included in one of the exclusions because it is known to also dilate.

CHAIRMAN PACKER: I guess we are saying we don't drive when it is raining, or something. I don't know.

DR. LIPICKY: Right. I'm not sure which, but be more explicit.

CHAIRMAN PACKER: What are the non-mortal adverse effect --

DR. LIPICKY: There is another complaint.

CHAIRMAN PACKER: What is that?

DR. LIPICKY: Another complaint.

DR. HORTON: Darlene Horton from Scios. Just a point of clarification. Were you only referring to IV vasodilators and Milrinone, or were you lumping Dobutamine into that statement?

We did not share with you that there are 44 patients who had gotten Dobutamine and Natrecor, this is in 325 and 326. And the safety profile reflects those patients in the greater data base. But there are fewer patients that received concomitant IV vasodilator therapy along with Natrecor.

DR. PIÑA: Yes, but they weren't on Dobutamine when you started the Natrecor drip. They couldn't have been on Dobutamine.

DR. HORTON: That is correct, I'm sorry, that is correct. They had Dobutamine added to Natrecor.

DR. PIÑA: They were clean until they started the Natrecor drip, and then someone added the Dobutamine, later on --

DR. LIPICKY: And you can start with the ED10 with Dobutamine.

DR. KONSTAM: I would not include Dobutamine in that list.

DR. LINDENFELD: Neither would I.

CHAIRMAN PACKER: We not only live in the ED90 universe, it may or may not be empiric universe.

I think there is a -- without belaboring this issue, because we could for quite some time, I think many of us would say that Dobutamine may or may not be a special case here, not because there is experience with it, but because its mechanism may not be potentiating of the vasodilator effects of the drug, which is the effect we are concerned about with respect to hypotension.

And I think that is the only guidance we can provide.

Eight, what are the non-mortal adverse effects of the drug; which, if any, are dose limiting; over what dose range are the effects seen, how do they compare to conventional therapy.

Marv?

DR. KONSTAM: You know, the only ones that I will bring out are hypotension, bradycardia, and renal dysfunction. And I think these are the ones that are concerning, to me, and over what dosing range?

I think they are seen over the dosing range that we've been looking at, the hypotension clearly appears to be dose related. And the others I can't quite tell.

And how does it compare to conventional therapy? I don't know how it compares to conventional therapy. I think that it is -- I'm struck by the fact that, for example -- I think I will just bring out, at this point, that I think the appropriate comparator, in my mind, of this agent is a pure vasodilator, and probably nitroprusside.

And so we actually don't have that. I mean, I think that the sponsor chose to go in the direction of comparison to conventional or standard care.

And I understand the rationale for doing that, but we are left without a comparator to the

agent to which it really should be compared. Because if you really want to know the answer to these questions you have to give it to comparing to a drug of comparable beneficial profile.

The one piece of data that I'm struck by, in this regard, if I remember it right, is in the small group of patients in 326 that was in the standard care group that received nitroglycerin, the incidence of hypotension -- of symptomatic hypotension I believe was non existent in that group, interestingly.

So, you know, looking at that, I mean I guess it seems to me that based on what we see here it may be -- the hypotensive problem may be considerably more.

And I think with regard to the other things I think that the bradycardia and the renal dysfunction are something special about this drug, relative to other hemodynamic agents.

CHAIRMAN PACKER: Well, I think nitroglycerin has a bradycardiac effect when people become hypotensive, which is thought to be reflex

mediated.

The sponsor actually refers to that effect being potentially -- it has been reported with nitroglycerin. Now, what is a little bit different about this drug, and someone help me out here, is that I think that the bradycardia with nitroglycerin is entirely related to patients who have hypotension.

And what wasn't exactly clear here was whether this is related to hypotension, or whether it was an additional effect of the drug. But there is a bradycardiac effect from nitroglycerin induced hypotension.

DR. COHN: It is kind of a vaso-vagel kind of response, visol-gerish, I guess.

DR. KONSTAM: I don't have any sense from the data set that that is what is going on here, with regard to the bradycardiac effect of this agent.

I'm not aware that the bradycardia had anything to do with the hypotensive patients. Was it -- these were separate adverse sets of adverse events, weren't they?

DR. HORTON: Yes, I think I can clarify a

little bit better. There were seven cases of bradycardia in the .015 group within the first 24 hours. But most of those cases lasted from one minute to fifteen minutes, they were self-limited. The heart rates were in the 50 range, somewhere down to 42, I believe, was the lowest heart rate.

One of those cases, two of those cases were associated with hypotension in the .015 group. In the .03 group there were nine cases, seven of which were associated with hypotension.

So in totality, with both doses, with the dose related effect on blood pressure with the higher dose you tend to get more bradycardia reported.

Now, I'm going to go out on a limb here and say that I think the reason why that is, is that when you are seeing gradual drops in blood pressure, say down to the 80 millimeter mercury range, and you are seeing the patient continuing to have a heart rate in the 50s, that gets reported as bradycardia.

Not necessarily because it is a dramatic bradycardia, I pointed out that most of these are sinus bradycardia, but it is just that physicians are

concerned that there is not a corresponding increase in heart rate, so it gets reported as a bradycardia.

CHAIRMAN PACKER: But your answer actually reinforces Marv's concerns that the bradycardia is independent.

See, the impression that we have is that the nitroglycerin bradycardia is hypotension related. The way that you've just responded to his question would suggest that the bradycardia is an independent effect here, which is not blood pressure mediated.

DR. RODEN: She said most of it is with hypotension.

CHAIRMAN PACKER: No, she said that people tend to report the brady --

DR. KONSTAM: We have to be careful because bradycardia can also cause hypotension. So I'm not -- and maybe I'm not sure what is going on here.

My sense of this is, you know, the point that you are making about the nitroglycerin is pretty unusual event, I would think. This isn't something that you see every time somebody gets hypotensive with

nitroglycerin.

And my sense of this, and if somebody wants to say, and particularly the clinicians over there, if they want to say we are wrong about this, we've got this wrong, is that the bradycardiac events that we are seeing are not some reflex response to the hypotension.

DR. GROSSBAR: We have argued that there is something about this product that, in a sense, does not produce as much of an increase in heart rate during the favorable hemodynamic response as others, and presented that in a favorable light, which is to say that it doesn't increase the rate pressure product and oxygen consumption.

I think we recognize that that isn't miraculous in some way, but it may be accompanied by some process, and we don't want to speculate on mechanisms, because we really don't know.

WE did a dog electrophysiologic study, it didn't reveal anything remarkable. We don't want to speculate on the mechanism, but the same mechanism that presumably preserves this heart rate from a

compensatory tachycardia may, in fact, lead to some of the observations you described.

DR. RODEN: I think it is important to, dealing with 8C here again, is to point out that there is really no way to compare this drug with conventional therapy like nitrates or nitroprusside.

Of course you don't see hypotension with those drugs because you titrate and back off, and you get an immediate return of blood pressure the moment you stop the infusion.

So you are using them in an entirely different way. Here you have a fixed dose which simplifies the regimen considerably, because you don't have to titrate, you just start that dose.

It may be that if one started nitroglycerin in ED50 dose, or ED90 dose, that you might actually see some of that bradycardia, but we don't give it that way.

So there is really going to be no way to make a direct comparison between conventional therapy and this therapy in terms of adverse effects such as hypotension.

CHAIRMAN PACKER: Okay. I think we've summarized it well. Does anyone have anything else to add?

(No response.)

CHAIRMAN PACKER: Nine. No deaths were observed during the double blind treatment period of Trials 311, 325, 326. During these trials respective following periods, there were 26 deaths, and there were a total of 34 deaths in the entire clinical data base.

How does drug affect mortality in acutely decompensated congestive heart failure? Marv?

DR. KONSTAM: We don't see any effect on mortality.

CHAIRMAN PACKER: Let me try -- are you saying that there is no effect on mortality, or one does not know what the effect on mortality is?

DR. KONSTAM: We don't see any effect on mortality. You know, I mean, I don't see anything in the data set to give me a hint that there is any effect on mortality one way or the other.

CHAIRMAN PACKER: Let me see if I

understand this. There are two possible answers here. There is either no effect on mortality, or there are, you can't say anything about the effect of the drug on mortality. That is one and two.

Which do you think it is?

DR. KONSTAM: I mean, we don't want to get into a discussion about equivalence trials, and whether this --

CHAIRMAN PACKER: No, no, we don't want to do that. I just want to know what your feelings are, one or two? One, that there is no effect of the drug on mortality; two we do not know what the effect of the drug on mortality is.

DR. KONSTAM: Big difference.

DR. MOYE: I'm going to try to rise to Marv's defense here. It is clear that this clinical program, this research program was not designed to look for mortality effect.

It doesn't have the resolving power it needs to be able to identify mortality effect. Having said that, we are not in a situation where all of the deaths occurred in one group or the other group.

There are no deaths.

CHAIRMAN PACKER: There are 34. No, that is after the follow-up period. I mean, you can look at the follow-up period, that would be fine.

DR. MOYE: I'm talking about the entire program.

DR. KONSTAM: How about if I answer the question this way. There is no effect on mortality to the level that raises my concern with regard to this agent.

CHAIRMAN PACKER: When you have no data how can you say anything about anything?

DR. COHN: -- unreasonable in their judgement, and this drug given for 24 hours, there is no reason why one would anticipate --

CHAIRMAN PACKER: Just suppose this drug were IV Milrinone, and I -- or PO Milrinone, or you know, PO - give me the most toxic drug you can think of. Flecainide. Any drug you want.

DR. RODEN: Let me tell you that in caps there was zero mortality signal when flecainide was

compared to placebo, none, zero, they were exactly the same number of deaths. So I think that the answer is that you have no data.

DR. KONSTAM: Well, that is what I've been saying.

CHAIRMAN PACKER: No. There is a difference between saying there is no effect on mortality than saying that you do not know what the effect of mortality --

DR. KONSTAM: We know the effect on mortality up to some certain limit that somebody would have to calculate in order to know. I don't know what that limit is.

DR. LIPICKY: Have you done that? Do you know what the upper 95 percent confidence limit would be on the odds ratio?

DR. GROSSBAR: Yes, versus placebo the 95 percent for an increase in mortality versus placebo is, I think, 1.8 percent.

DR. LIPICKY: 1.8.

DR. GROSSBAR: Greater than placebo, 95 percent.

DR. LIPICKY: Right.

DR. GROSSBAR: And I think versus active control it is about 3.6 percent, or something like that. 3.8 percent.

CHAIRMAN PACKER: We can make this very, very clear, and try to put this into proper perspective. If the division wanted to put something in the labeling about mortality, would the wording be, this drug has no adverse, or this drug has no effect on mortality, or would the labeling be the effect of this drug on mortality is unknown?

DR. KONSTAM: I don't think --

DR. LIPICKY: I would have a third alternative, that there could be wording that says that there are insufficient numbers of deaths in the studies to have a good estimate that --

CHAIRMAN PACKER: It is the same as saying that the effect on mortality is unknown.

DR. LIPICKY: That the upper 95 percent confidence limit odds ratio was 1.8 for placebo, so it could be as great as --

CHAIRMAN PACKER: Okay. So there are

three possibilities.

DR. LIPICKY: Or it could be as low as --

CHAIRMAN PACKER: Right. The three possibilities are: One, saying that there is no adverse effect, or favorable effect on mortality; Two, that the number of deaths was very, very small, and the confidence intervals range from whatever it is to whatever it is. And third, the effect on mortality is unknown.

That is it, there are three possibilities. Let's vote. We'll just reiterate what they are so it is clear.

One is there is no adverse -- no favorable or adverse effect on mortality. Two, there are very few deaths, here is the point estimate in the confidence intervals. Third, we do not know anything about the effect on mortality.

Joann?

DR. LINDENFELD: I would go for the third. The effect on mortality is unknown.

CHAIRMAN PACKER: Lem?

DR. MOYE: 2.

DR. PIÑA: 2.

DR. RODEN: 3.

DR. GRABOYS: 3.

CHAIRMAN PACKER: 3. Okay. Ten, when administered for the treatment of acutely decompensated heart failure how does the drug and conventional therapy, respectively, affect patients overall hospital stay, stability after discharge from the hospital, worsening of heart failure, incidence of re-hospitalization for congestive heart failure.

Marv, this probably shouldn't take that long.

DR. KONSTAM: I don't think there is any observed effect on any of these things.

CHAIRMAN PACKER: Does anyone disagree?

(No response.)

CHAIRMAN PACKER: Eleven, this is a peptide metabolized by intracellular proteolysis and by cleavage, by neutral endopeptidase. Have there been sufficient studies of pharmacokinetic drug interaction to reassure you that important drug interactions are unlikely to emerge with broader

exposure.

We will go to Marv and then Dan on this. Sorry, Dan. Marv?

DR. KONSTAM: Let's see, have there been sufficient studies to reassure me?

CHAIRMAN PACKER: Yes.

DR. KONSTAM: No, there have not been.

CHAIRMAN PACKER: Dan?

DR. RODEN: I'm not even sure what an inhibitor of a neutral endopeptidase would look like. I'm sure there are such things, and it is up to the Army pharmacokineticist to tell me whether those studies have been done, I guess.

DR. LIPICKY: They haven't been.

DR. RODEN: They haven't been or such things don't exist?

DR. LIPICKY: There haven't been, but we don't -- I guess I should also add we wouldn't know what to do.

DR. RODEN: So there is just no data.

DR. LIPICKY: But we were looking to you.

DR. RODEN: Well, it is like looking in a

mirror, isn't it?

CHAIRMAN PACKER: 12. Should Nesiritide be approved for the short term, less than 24 hours intravenous in-hospital treatment of acutely decompensated chronic congestive heart failure.

And let me just emphasize the operative words here. Short term, less than 24 hours, in-hospital, acutely decompensated chronic heart failure. I guess that makes the issue about acute MI, takes into consideration the lack of data of acute MI.

And why don't we vote on that before we go to the if-sos. Marv?

DR. KONSTAM: I'm going to vote no, and I find it a very difficult decision, but let me just go a little bit into my reasoning.

You know, I guess the standard for approval is efficacy and safety, and I'm confident about the efficacy of this drug. There are safety issues, and I guess in the end it becomes a judgement call about whether the safety issues are sufficient to prevent approvability. And then there are also usage issues.

And I think there are concerns about both of those. Let me just first say, in general terms, I guess I then, you know, trying to get that cost benefit analysis into my own personal judgement, I am influenced by the relative role of particular agent compared to other agents that are available.

And I don't see any evidence here that this agent is better than available intravenous vasodilator agents. I don't see that anywhere in the data set.

Nor do I have a strong suspicion that that is the case, based on the data set.

And so given that I guess I tend to be very sensitive to the concerns that I have, and I have a number of them. I think the adverse effects that we've talked about continue to be concerning. Hypotension is not concerning in and of itself, in a vasodilator, but this is clearly not an ideal situation in terms of the rapid offset of the potential hypotensive effects.

The renal dysfunction is confusing to me. I think there is some level of renal dysfunction, I'm

not sure why it is occurring, I'm not sure in whom it is occurring, I'm not sure precisely what the long term consequences of it might be. Maybe it is okay, but the data set is too small to really reassure me of that.

The bradycardia is there. Again, I don't quite understand it. The fact that I don't understand some of these adverse effects just raises my anxiety level about them.

And then there are a number of unknowns. We talked about the dose response. I probably could get myself to a level of acceptance of what we know about the dose response, but it is a little bit of a question mark.

Again, there are no comparative data with other vasodilator agents, precisely, and we talked about the fact that there are not -- there is virtually no data about concomitant use of other intravenous vasodilator agents.

We can say that it would be contraindicated, but the usage out there will seep in, and we don't have any information about that, at all.

And let me just add one final point, which really hasn't been brought up until now.

You know, when I use intravenous inode dilators, let's call them for lack of another word, in a setting of acutely decompensated heart failure, frankly one of the reasons I'm doing that is to facilitate diuresis and retain renal function.

And that is really, and it has been said that usually these patients are on diuretics because you are trying to diurese them, and so it is not yes, lower wedge pressure, but we really haven't talked about the fact that one of the key reasons for using these agents is to facilitate diuresis while protecting renal function.

And I, based on what I see here, I would not use this drug compared to the other drugs that I have.

So for all those reasons, at this point, I would vote no.

CHAIRMAN PACKER: Ray?

DR. LIPICKY: Can I argue with you for just a moment? The basis of approval usually is that

the drug in question is better than nothing at all. And there is rarely a requirement that to approve a drug it needs to be better than something other than placebo.

With the exception being that when there is some adverse effect, that may be very worrisome, one might then say the other drugs that are available for treatment don't have that adverse effect, and consequently would only make sense to use the new one if, in fact, it had an advantage over any of the ones that were there.

And then one would want a head to head comparison that actually may have some demonstrated advantage. It isn't clear to me that what you said puts this in the category where there is some adverse fact that would put this in that category, and then you are just kind of making a value judgement about what else is there, and that shouldn't be part of your thinking process, I don't think.

DR. KONSTAM: Right. My sense is that my opinion without the data is that it probably isn't in that category. And I can go through why.

DR. LIPICKY: Well, that is okay, but you don't have the data. And you should only be making your decision on the basis of whether or not this is better than nothing.

DR. KONSTAM: Well, I mean, I followed your logic up until that point. I mean, I'm with you in terms of, you know, I understand the criteria for approvability, and so that is why I went through it.

I mean, I think that there are safety concerns here. We don't have the data that I would like to see, specifically, which is a head to head comparison between this agent and nitroprusside.

DR. LIPICKY: And what would you require for that?

DR. KONSTAM: I'm sorry?

DR. LIPICKY: Let's say you were designing a trial that was head to head, Nesiritide versus nitroprusside.

DR. KONSTAM: Right.

DR. LIPICKY: On what basis would you make the decision that now it was approvable?

DR. KONSTAM: I would design a trial that

would achieve comparable efficacy of two -- of the two vasodilating agents.

DR. LIPICKY: How would you -- for wedge pressure?

DR. KONSTAM: I would go for wedge pressure with effects confirmed by symptomatology.

DR. LIPICKY: And you think that you would be able to design the equivalence of a non-equivalence trial using wedge pressure as an endpoint?

DR. KONSTAM: Well, the purpose of the --

DR. LIPICKY: How would you get -- so let's say the two drugs were within one millimeter of mercury wedge pressure, millimeter, is that good enough?

DR. KONSTAM: Yes.

DR. LIPICKY: Well, you would never get that, right? How would you get that?

DR. KONSTAM: I'm not concerned about this drug beating nitroprusside in efficacy.

DR. LIPICKY: But how would you know they are equivalent in efficacy; what measure would you use?

DR. KONSTAM: Okay, well I just said it. You want me to specify within what range of wedge pressure?

DR. LIPICKY: Well, clearly, because okay, how would you know you had equivalent efficacy, would one millimeter mercury wedge pressure, when, at what time?

DR. KONSTAM: Well, we could work those questions out. I don't know whether you want me to commit myself on that right now.

DR. LIPICKY: Well, but you really think you could?

DR. KONSTAM: Yes, it has been done before, and it has been in other -- there have been other comparative hemodynamic studies where agents effects on hemodynamics were matched, and they have been done fairly successfully.

I don't know whether -- I don't know how to answer the question in terms of within how many millimeters of mercury wedge pressure, of the top of my head.

DR. LIPICKY: Did the successful trials

did that? I mean, they had some specification for millimeters of mercury at some point in time?

DR. KONSTAM: Probably.

DR. LIPICKY: Of the 24 hour day? I doubt it. You eyeball the data and say it looks the same.

DR. KONSTAM: I'm not sure what you are asking, Ray.

DR. LIPICKY: Well, I don't think you can get a trial like you want.

DR. KONSTAM: I do.

DR. LIPICKY: Okay.

DR. KONSTAM: But let me -- I mean, if you want to ask what trial I would like to see to get me to the level of approvability, that would be the trial I would design. I think we are still faced right now with approval or not.

And let me just say that, you know, I'm really at the point that you described, without the data. That is to say that I -- we have other vasodilator, we have nitroprusside, and without having the data in front of me, I'm going to go so far as to say that I'm concerned that this drug is less safe

than nitroprusside.

With regard to the hypotensive effect I think it is going to be comparable, but nitroprusside is probably an easier drug to titrate than this drug.

And with regard to the renal insufficiency, and the bradycardia, I'm not aware that that is going to be a concern for me with nitroprusside.

So without the data comparatively, but with the significant, you know, history of clinical use of the agent, that is where I am.

CHAIRMAN PACKER: Tom, do you want to start?

DR. GRABOYS: I think it is really coming down to the wire, and kind of agonize back and forth on it. But I think the drug does expand our therapeutic modalities for treating this problem, which is of significant magnitude, and I would vote for approval.

CHAIRMAN PACKER: Dan?

DR. RODEN: I agree with everything that Marv says, but I'm going to vote for approval. I'm a

yes.

CHAIRMAN PACKER: Cindy's vote is yes. Joann?

DR. LINDENFELD: I would vote yes. I don't have -- I agree with everything Marv said but I think the drug is effective, and I think it would help us, so I vote yes.

CHAIRMAN PACKER: Lem?

DR. MOYE: I vote no. I agree with what Marv has said, and I have some serious reservations about the protocol, and the design of this study, which makes me wonder whether in fact this medication is better than placebo.

CHAIRMAN PACKER: Ileana?

DR. PIÑA: I've been back and forth in my own mind, and I think I'm coming down on Marv's side, I'm going to agree with Marv, I'm going to say no.

CHAIRMAN PACKER: Vote is no. What is the vote so far?

DR. LIPICKY: Don't tell them, Joan.

CHAIRMAN PACKER: Four yes and three no? It doesn't matter.

My own sense, I think there are a lot of deficiencies in this data base. I think that there are real concerns about the -- I'm personally concerned about the lack of acute MI data. I think the drug is going to be used in acute MI, and I think that we need that kind of data.

I'm concerned about a number of the confounding issues with respect to symptoms. I'm concerned, I think, about the fact that I guess of all the side effects the one that puzzles me the most is the renal issue, which I don't understand.

And I wish I understood better, and it might just require more patience to understand it better. And you know I must say I'm not certain I share Marv's concerns, because I really think that I would like to view this drug on its own merits, and not so much how it compares to available agents.

That is really going to be determined by the marketplace, and physician's use of the drug. And I just think there is a lot of other questions and issues that the sponsor could have addressed.

Having said that I guess I would agree

with Tom that there is something that this drug may do for patients that isn't available right now. I view this as being an extremely close call, but I guess I would come down and say yes.

DR. LIPICKY: So then you have to continue.

CHAIRMAN PACKER: You have 5/4 in favor? 5/3.

DR. LIPICKY: So you have to answer the rest of the questions.

CHAIRMAN PACKER: Now you have to answer the rest of the questions.

What dosing regimen should be specified for use -- Marvin, it is going to be hard for you to answer these questions.

DR. KONSTAM: Well, I didn't read past here, okay? I think this is one of the concerns. I'm not quite sure, now I see whether I'm a ED90 or a 10 guy. I think the dose that is being recommended is the .015 dose.

I think that is reasonable. I'm not sure how to titrate it above and below that dose. I think

it would be reasonable to recommend a dose half that amount, and titrate it up.

Again, the problem there is we don't know anything about titration in clinical practice. So that is my answer. Did I answer?

CHAIRMAN PACKER: 0.15.

DR. KONSTAM: 0.015.

CHAIRMAN PACKER: 0.015 I guess up to 0.03? No. I'm sorry, forgive me, summarize?

DR. LIPICKY: Paraphrasing Marvin's statements one would put in the dosing instructions the doses that were studied and say, use your best judgement.

CHAIRMAN PACKER: Okay. And the clinician should do that based on whatever they do to make the decisions that they make?

DR. LIPICKY: However they make decisions.

CHAIRMAN PACKER: Does anyone disagree with that?

DR. RODEN: Ray, I still think you ought to have a chance to look at the PKPD data as they emerge, and see if there is any suggestion that we

ought to reconsider that, and I actually would be in favor of recommending a bolus, because that is the regimen that was used.

CHAIRMAN PACKER: Let's move forward to 12B. What level of care should be recommended? Sponsor is seeking claim for being able to infuse this without a catheter in place. How does the Committee feel about this? Marv.

DR. KONSTAM: Yes, my feeling about this is that there is likely to be significant risk if the drug is infused in patients with normal wedge pressures. I think that is, to me, the real issue here, the principal issue here.

And you know, I don't know how to come down on that. I mean, I would feel sympathetic to some commentary to that effect. And saying that, you know, if there is any question based on clinical assessment, that the wedge pressure is normal then a Swan has to go in before it is used, rather than requiring that Swans routinely be used.

CHAIRMAN PACKER: So your vote is to say that invasive monitoring should be carried out?

DR. KONSTAM: No. What I said is that I think the drug should be used where there is a degree of clinical certainty that we are dealing with a patient with a high wedge pressure.

CHAIRMAN PACKER: How would one know that?

DR. LIPICKY: When you are in doubt, go to a Swan.

DR. KONSTAM: There are patients in whom you can be absolutely confident you are dealing with a high wedge pressure. And if I had that patient in front of me, and I knew it, I would feel comfortable using the drug in that situation.

CHAIRMAN PACKER: Okay. Dan?

DR. RODEN: I think given all the uncertainties about the drug, and the use of the drug, and the regimen we should use, and whether it is actually predictable that hypotension will or won't occur, and the sense that there were certainly some patients screened for the drug, for whom the pharmacist mixed up a drug, and then they were found not to have wedge pressures in the qualifying range, I would actually insist that they have a pulmonary

catheter in place.

CHAIRMAN PACKER: We have two different recommendations. Does anyone have yet another different recommendation, so that we can take a vote? Tom?

DR. GRABOYS: Can it be in the package insert that the manufacturer strongly urges the use of invasive hemodynamic monitoring?

DR. GROSSBAR: I just want to remind the Committee, the day is long, that the vast majority of the patients you've been discussing from the safety point of view were derived from a study where there was no invasive hemodynamic monitoring.

You are inferring, a lot of information about symptomatic hypotension, and your worst case or your fears are based on patients who were not, in fact, monitored for their wedge pressure before they were treated.

So, I don't know, necessarily whether that pulls one side or the other, but I just wanted to remind you that 200 plus of the patients were from --

DR. KONSTAM: Can I go with that? Would

you agree with me that the biggest safety concern with regard to hypotension would be in patients with normal wedge pressures in whom this is given to?

DR. GROSSBAR: I'm not a cardiologist, and I'm not sufficiently expert to make that judgement. But I would say that I think that the same tools that people use, to use these other drugs which have been, I think, cavalierly described as we know how to use it, we just do this, and everything works out, is not really necessarily of what actually happens.

When I've read papers on nitroprusside for the treatment of post-operative hypotension, there is a lot of hypotension reported there. So maybe you can get rid of it fast, I can't quarrel with that, but it happens.

So I think we don't know anything more than what we've tested. I'm sure even if we said we did, Dr. Lipicky wouldn't let us say it anyway, so it doesn't really matter if we speculate on it.

CHAIRMAN PACKER: Okay. Let's take a vote. The vote is I guess three choices. One, there should be no -- the general way that it is done right

now is, or I shouldn't say the general way it is done right now.

One way which is commonly -- that commonly appears in labeling is it should be infused under close supervision. I think the sponsor actually is proposing something like that, so that is choice number one.

Choice number 2 is Marv's recommendation, which is close supervision plus the clinical assurance or belief, or whatever the word is, that feeling pressures are elevated.

And the third is invasive monitoring.

Marv, do you want to lead us off? Or is that two? Joan, we will go around this way.

DR. LINDENFELD: I like Marv's statement, I think two. I'll go with Marv, 2.

CHAIRMAN PACKER: 2. Lem?

DR. MOYE: I think Marv is right again. 2.

DR. PIÑA: 2.

DR. GRABOYS: 3.

DR. RODEN: 2.

CHAIRMAN PACKER: I will vote 3. Only because the fact that, you know, I think we need to know more about the drug, and until we know more about the drug I would like to see the patients be as carefully monitored as possible. That is the only reason I vote 3.

But what was the vote? There were two 3s, and the rest were 2s. And Cindy I think votes essentially -- well Cindy did not have the option of Marv's choice, so she did not favor invasive monitoring, so I think that would be the only thing we could say from what she has said.

DR. LIPICKY: I need to ask one question that you guys know the answer to. Somewhere didn't we, in the back of my mind, I remember there was a trial that said that people with heart failure who had Swan-Ganz in and who did not, were able to be differentiated.

CHAIRMAN PACKER: It wasn't a trial, it was a case control study with a relative risk of 1.24.

DR. LIPICKY: Thank you, okay.

CHAIRMAN PACKER: We've already had a

Committee meeting in the past as to whether in a case control study with a relatus of 1.24 means. It wasn't last night, no.

CHAIRMAN PACKER: 12C, what warnings or precautions should be emphasized in the package insert?

DR. LIPICKY: I have that from you guys already.

CHAIRMAN PACKER: Terrific. Can I make a recommendation that we skip 13. There are two reasons for making that recommendation. One is the lateness of the hour, so I'm not exactly certain when we will have the vigorous discussion this question deserves.

More importantly I'm not exactly certain that the global issues that are reflected in 13 are most appropriately discussed in the context of this NDA.

DR. LIPICKY: Right.

CHAIRMAN PACKER: So we will take a rain date on question 13.

DR. LIPICKY: But on your way home, or at least tonight I would like you to lose a little bit of

sleep, as you contemplate why you were willing to take action, bunches of actions on side effects, right? And you even concluded that hypotension was dose related.

You never asked the question was this an intent to treat analysis, you never asked the question was this a pre-specified endpoint? You never came to any kind of -- you never agonized over whether you could believe the data because it must have fit your model.

I just want you to lose sleep.

DR. MOYE: We agonized about those from the inception of the conversation today, even about the main discussions.

CHAIRMAN PACKER: We will take Ray's advice and guidance, and the meeting is adjourned.

(Whereupon, at 4:00 p.m. the above-entitled matter was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: 87TH MEETING

Before: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

Date: JANUARY 29, 1999

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Donna Willis

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