

UNITED STATES  
3607 '99 MAR 12 P1:06  
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

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

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

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

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

11 SECRETARY STANDAERT: The following  
12 announcement addresses the issue of conflict of  
13 interest with regard to this meeting, and is made a  
14 part of the record to preclude even the appearance of  
15 such at this meeting.

16 Based on the submitted agenda for the  
17 meeting, and all financial interests reported by the  
18 Committee participants, it has been determined that  
19 all interest in firms regulated by the Center for Drug  
20 Evaluation and Research present no potential for an  
21 appearance of a conflict of interest at this meeting,  
22 with the following exceptions.

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

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

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

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

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

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1 be here today.

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

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

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

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

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

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1 analysis of the data.

2 In the event that the discussions involve  
3 any other products or firms not already on the agenda,  
4 for which an FDA participant has a financial interest,  
5 the participants are aware of the need to exclude  
6 themselves from such involvement, and their exclusion  
7 will be noted for the record.

8 And that concludes the conflict of  
9 interest statement for today.

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

12 (No response.)

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

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

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

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1 application for this product in April of 1998.

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

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

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

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

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



1 CHF.

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

6 The scientific name for Natreacor is human  
7 B-type natriuretic peptide, or hBNP. In the literature  
8 hBNP is sometimes referred to as brain natriuretic  
9 peptide. The proposed USAN name, currently under  
10 consideration, is Nesiritide.

11 SCIOS utilizes a recombinant manufacturing  
12 process to produce the 32 amino acid peptide product  
13 with the trade name Natreacor.

14 SCIOS has demonstrated that Natreacor is  
15 chemically and structurally identical to endogenous  
16 hBNP.

17 The IND for Natreacor was filed in November  
18 of 1993. Clinical development commenced in January of  
19 1994, and an end of phase II meeting was held in July  
20 of 1996, and the clinical pre-NDA meeting took place  
21 in July of 1997, and finally as I stated earlier,  
22 SCIOS filed the Natreacor NDA in April of 1998.

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

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

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

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

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

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

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

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

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

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

22 It is also relevant, in that regard, to

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

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

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

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

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

22 These are the topics I will be discussing

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

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

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

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

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

6           Human B-type natriuretic peptide, or HBNP,  
7 is a 32 amino acid peptide synthesized by the  
8 ventricular myocardium. Plasma BNP levels are elevated  
9 in patients with heart failure with both systolic and  
10 diastolic dysfunction.

11           And BNP is believed to be one of the  
12 body's own natural compensatory mechanisms in response  
13 to cardiac dysfunction.

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

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

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

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

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

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

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

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

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

11 In each study the effects of placebo on  
12 wedge are shown in blue, and the effects of Natreacor  
13 at the various doses studied in each study are shown  
14 in yellow.

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

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

22 Study 307 was a randomized double blind

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

5 The doses of Natreacor administered are  
6 shown here on the X axis, and they were 0.003, 0.01,  
7 0.03, and .1 microgram per kilogram per minute. So  
8 you can see this study covered a wide range of doses.

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

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

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

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

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

13          And these doses were studied extensively  
14          in subsequent clinical studies.

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

22          The vast majority of patients had NYHA

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

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

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

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

17 Both protocols required that at enrollment  
18 patients have a pulmonary capillary wedge pressure of  
19 at least 18, and a cardiac index less than or equal to  
20 2.7.

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

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

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

8 The doses of Natreacor administered in  
9 study 311 are 015, 03 and 06 micrograms per kilogram  
10 per minute. And in study 325, the 015 and 03 doses  
11 were administered.

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

21 For patients randomized to the Natreacor  
22 group in study 325, the duration of Natreacor

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

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

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

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

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

22 Now, it should be noted that both of the

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

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

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

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

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

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1 forward methodology, or by the protocol specified  
2 analysis methodology.

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

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

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

21 You can see that Natreacor had sustained  
22 effects on hemodynamic parameters through the 24 hour

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

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

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

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

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

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

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

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

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

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

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1 status.

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

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

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

16 Thus, Natreacor has been shown to improve  
17 clinical status when compared to placebo, when  
18 assessed either by the subjects themselves, or by  
19 their physicians.

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

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1 headedness, and decreased appetite.

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

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

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

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

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

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1 of the three rating categories.

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

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

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

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

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

22 Now, up until now I've been talking about

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

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

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

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

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

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

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

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

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

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1 actual clinical practice.

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

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

12 A Swan-Ganz catheter was used in less than  
13 20 percent of patients enrolled in this study.

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

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

22 Treatment assignment was open label as to

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

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

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

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

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1 review those with you.

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

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

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

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

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

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

4 Thus this is really looking at Natreacor as  
5 the sole vasoactive agent for the treatment of these  
6 patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

18 Highly statistically significant results  
19 were obtained for the primary efficacy endpoint of a  
20 reduction in wedge in both pivotal efficacy studies  
21 311 and 325.

22 In addition, these studies have shown that

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

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

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

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

16 The last topic I will discuss this morning  
17 is our recommendations regarding dosing. And as I  
18 mentioned, we are recommending that Natrecor be  
19 administered as a fixed dose infusion of a dose of  
20 0.015 micrograms per kilogram per minute without a  
21 preceding loading bolus.

22 And I will now review the rationale for

1 each of those recommendations.

2 First, with regard to the doses, as I've  
3 mentioned, Natreacor has been studied over a wide dose  
4 range, ranging from .003 to .1 micrograms per kilogram  
5 per minute. But doses in the range of 0.15 to 0.3  
6 appear to be the optimal dose range for patients with  
7 CHF, and therefore these two doses were studied  
8 extensively in the phase III program.

9 And both of these doses were efficacious  
10 by all of the criteria assessed. Both doses achieved  
11 highly statistically significant effects on the  
12 primary efficacy endpoint of reduction in wedge  
13 pressure in both pivotal efficacy studies, 311 and  
14 325.

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

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

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1           When you look at the effects of the two  
2 doses on clinical status and symptoms, you may have  
3 noticed, however, that the 03 dose did not seem to  
4 result in a more marked clinical response than did the  
5 015 dose.

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

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

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

22           I will now discuss the rationale for our

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

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

10 Now, this is showing the results of study  
11 305, which is a study in which individual bolus doses  
12 of Natrecor were administered to patients with CHF,  
13 and the effects on hemodynamics were followed for four  
14 hours.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. ALLGREN: Right.

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

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

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

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

21 DR. KONSTAM: One day?

22 DR. ALLGREN: Yes.

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

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

6 DR. KONSTAM: In 325?

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

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

13 DR. ALLGREN: Right, right.

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

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

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

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

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

14 DR. KONSTAM: Okay. Now, I just wanted to  
15 ask you about dose response, and particularly it looks  
16 a little different than 311 and 325, wherein 311, you  
17 know, I don't see a clear dose response between the  
18 .015 and .03. In fact, depending on how you slice it,  
19 and the different graphs, it looks like it is actually  
20 the other way, it looks like -- the two doses look  
21 either equivalent, or in fact the 015 looks better.

22 DR. ALLGREN: Yes, we noticed that as

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

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

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

21 DR. ALLGREN: About three to six hours.

22 DR. KONSTAM: Three to six hours. Can you

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1 explain that?

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

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

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

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

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

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

19 DR. ALLGREN: Yes.

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

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1 subjective call.

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

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

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

19 DR. KONSTAM: Right.

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

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

4  
5 So that would contribute to somewhat of a  
6 trend of these curves appearing to taper off at the 24  
7 hour time point.

8 DR. KONSTAM: Well, I guess, you know, for  
9 what it is worth, I guess that the -- one of the  
10 questions to ask is, is there a sustained effect, yes  
11 or no. And I'm still not -- I mean, it seems -- my  
12 read quick, is that there is a sustained effect, but  
13 I'm not sure that we are not beginning to lose it at  
14 24 hours.

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

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

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1 the drug on hemodynamics through that time point.

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

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

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

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

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

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1 study coordinator.

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

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

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

14 DR. ALLGREN: Yes, they would have been.

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

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

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1 response at the time they were filling it out.

2 DR. ALLGREN: One thing to keep in mind is  
3 that very similar response rates were seen in study  
4 326, where most patients did not have a Swan-Ganz  
5 catheter.

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

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

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

22 DR. ALLGREN: The way it was supposed to

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

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

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

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

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

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

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

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

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

17 Tom?

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

22 DR. ALLGREN: In study 325. But as I

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

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

7 DR. ALLGREN: Pardon me?

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

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

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

17 DR. ALLGREN: Right.

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

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

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1 six hour period, the first six hour period.

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

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

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

9 DR. ALLGREN: No, across the groups.

10 DR. GRABOYS: Okay.

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

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

15 CHAIRMAN PACKER: You have to say your  
16 whole name.

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

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

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

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

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

10 And, in fact, if you look at the average  
11 baseline numbers, this is a moderately sick group of  
12 decompensated heart failure patients with wedge  
13 pressures around 25 to 30, and cardiac indexes around  
14 1.7 or 1.8.

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

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

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

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

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

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

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

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

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

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

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

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

11                   DR. ALLGREN: Uh hum.

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

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

19                   Joan?

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

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

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

6 DR. ALLGREN: Diuresis in --

7 DR. LINDENFELD: A total amount.

8 DR. ALLGREN: Are you interested in -- you  
9 are saying Natreacor's diuretic properties, or are you  
10 saying --

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

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

17 DR. LINDENFELD: Just in understanding the  
18 patients, these patients were in the hospital for the  
19 24 hours. They all -- did they all get diuretics,  
20 they were all acutely decompensated?

21 DR. ALLGREN: Which study are you  
22 referring to?

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1 DR. LINDENFELD: 325, I'm sorry.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 having acute MIs.

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

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

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

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

17 DR. ALLGREN: During the study?

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

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

21 CHAIRMAN PACKER: Jay?

22 DR. COHN: I am sorry I missed the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 CHAIRMAN PACKER: Ray?

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

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

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

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

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

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

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

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1 emphasized now going back to 1987.

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

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

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

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

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

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

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

3 CHAIRMAN PACKER: Okay. Bill, brief.

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

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

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

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

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

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

8 CHAIRMAN PACKER: That, actually, is the  
9 problem.

10 DR. ABRAHAM: Yes.

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

16 Ileana, why don't you begin?

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

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

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

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

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

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

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

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

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

3 DR. ALLGREN: In study 325 it was in the  
4 range of around 1.2. I mean study 326 it was around  
5 1.2.

6 DR. LINDENFELD: Serum sodium?

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

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

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

13 DR. LINDENFELD: At baseline?

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

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

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1 pressure.

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

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

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

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

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1 us.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20

21 Now, the second -- pardon me?

22 DR. MOYE: Excuse me, that first circle

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 three hours.

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

9 CHAIRMAN PACKER: Lem?

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

16 DR. ALLGREN: In the second population --

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

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

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1 none of those errors happened in placebo patients.

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

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

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

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

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

13 DR. KONSTAM: O, I see.

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

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

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

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

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

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

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

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

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

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1 in that 29?

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

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

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

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

14 DR. LINDENFELD: If they had --

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

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

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

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

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

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

22 DR. LIPICKY: But it was not.

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

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

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

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

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

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

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

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

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

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

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

21 DR. MOYE: Okay. And therefore --

22 DR. LIPICKY: After they were through with

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1 their analyses.

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

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

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

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

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

22 I would say, though, that again there is

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

5 CHAIRMAN PACKER: Marv?

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

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

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

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

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

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1 make it.

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

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

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

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

22 That is that it should be as likely to

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

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

10 But when you see the numbers that Joan  
11 pointed out, you know, 29 and there is 7 missing, or  
12 9 missing, whatever; and it could be that it is just  
13 presented in a misleading way.

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

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

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1 the small P value.

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

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

14 DR. MOYE: Right, right.

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

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

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

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

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

8 CHAIRMAN PACKER: I see.

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

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

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

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

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

22 And then some of these have to do with

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

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

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

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

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

22 DR. LIPICKY: Did someone have to put drug

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1 into a vial?

2 DR. ALLGREN: It is D5W is the placebo.

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

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

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

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

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

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

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

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

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

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

5 DR. ALLGREN: The pharmacist knew.

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

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

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

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

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

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

5 DR. GROSSBAR: Pharmacy records.

6 DR. COHN: Just the records?

7 DR. GROSSBAR: Right.

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

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

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

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

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

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

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

8 DR. ALLGREN: Right.

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

11 DR. PIÑA: Or hypotension.

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

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

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

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

3 DR. ALLGREN: Not necessarily, no.

4 DR. KONSTAM: That didn't happen?

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

8 DR. KONSTAM: Okay, I got it.

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

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

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

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

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

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

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

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

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



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

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

7           Why did you choose 24 hours in your  
8 clinical trial design? Because if one really wanted  
9 to make sure that this was a different effect than  
10 nitroglycerin, which generally develops tolerance in  
11 48 hours, or between 24 and 48 hours, one would have  
12 liked to have seen the effect persist at up to 48  
13 hours in order to show that what is going on here is  
14 not an attenuation of effect, and is different than  
15 what may have been reported in the past with A&P or  
16 nitroglycerin.

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

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1 placebo arm.

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

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

10 CHAIRMAN PACKER: Dan?

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

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

19 DR. ALLGREN: Slide 21?

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

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1 higher dose?

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. ALLGREN: In slide --

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

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1 can eliminate this as a bolus effect.

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

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

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

12 DR. ALLGREN: Pardon me?

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

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

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

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1 which may partially explain these effects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 CHAIRMAN PACKER: Dr. Karkowsky?

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

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1 pretty much gone.

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

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

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

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

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

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

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

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

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

13 DR. RODEN: I understand.

14 CHAIRMAN PACKER: Marv?

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

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

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

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

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

15 DR. ALLGREN: Pardon me?

16 DR. LIPICKY: Nothing.

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

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

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1 many patients we have measurements on with and without  
2 bolus.

3 DR. ALLGREN: In that particular study,  
4 study 306 had about 8 patients per group, and study  
5 325 had about 42 patients in the group.

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

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

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

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

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

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1 3,000, and for the second group about 3,700.

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

4 CHAIRMAN PACKER: And the levels on  
5 placebo?

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

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

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

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

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

7 DR. RODEN: I understand what you are  
8 saying. So these are concentrations with a bolus,  
9 without a bolus, since the half life was 20 minutes,  
10 without a bolus you would expect steady state in about  
11 100 minutes, or one and a half hours.

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

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

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

22 DR. SAMBELL: I think your terminal half

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

5 DR. RODEN: Well, the FDA document says 20  
6 minutes, and you can split hairs about when you are at  
7 90 percent.

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

15 And, in fact, the curve we did very  
16 frequent measurements of hemodynamics early in the  
17 course of that study, the curve begins to drop within  
18 15 minutes. The 15 minute time point is already done  
19 without a loading bolus.

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

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1 Dan?

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

7 DR. ALLGREN: Slide 24?

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

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

17 DR. ALLGREN: These were the four.

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

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1 DR. ALLGREN: Right.

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

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

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

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

17 CHAIRMAN PACKER: It depends on what is,  
18 is.

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

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1 hemodynamics.

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

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

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

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

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

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1 which of those two that they were on.

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

10 DR. ALLGREN: Right.

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

13 DR. ALLGREN: Right.

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

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

22 DR. ALLGREN: Right, but not --

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

4 DR. ALLGREN: Right.

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

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

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

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

22 And this makes it really difficult. I

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

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

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

10 DR. ALLGREN: Date wise?

11 CHAIRMAN PACKER: Yes.

12 DR. ALLGREN: I have to look that up.

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

17 DR. ALLGREN: Yes, that is --

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

21 DR. ALLGREN: Yes, that sounds right.

22 CHAIRMAN PACKER: So the -- but when did

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1 recruitment begin?

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

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

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

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

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

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1 going on.

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

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

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

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

22 And then the patient gets the impression

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

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

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

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

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1 hypotension than placebo.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 significance, and clinical significance.

2 For example, I'm not sure we would think  
3 that it is really all that meaningful that fewer than  
4 25 percent or 30 percent, 27 percent of patients had  
5 appetite improved, but yet it is statistically  
6 significant in one of the dose groups.

7 Still the more --

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

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

22 And, you know, I think that it is correct

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

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

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

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

19 CHAIRMAN PACKER: Jay, actually you were  
20 first.

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

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

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

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

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

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

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

16           DR. COHN: Or the code was broken.

17           CHAIRMAN PACKER: Bill?

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

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1 two studies in regard to symptom assessment.

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

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

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

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

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

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

10           DR. ALLGREN: Which slide are you --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12           Cindy?

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

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

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

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

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

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

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

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

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1 DR. PIÑA: Some of them were.

2 CHAIRMAN PACKER: How many were dyspnea at  
3 rest?

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

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

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

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

16 We did do --

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

19 CHAIRMAN PACKER: Okay, I think. Ray?

20 DR. LIPICKY: That is okay, I think.

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

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

6 I mean, it is just a semantic thing.

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

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

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

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

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1 close.

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

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

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

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

21 CHAIRMAN PACKER: All right.

22 DR. LIPICKY: Maybe it is worth a minute

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

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

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

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

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1 coals.

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

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

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

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

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

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

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

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

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

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

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

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

6 Now, whether how to asses those symptoms,  
7 which symptoms to asses, what the problems are, which  
8 patient population; the nice thing about it is that  
9 each drug presents its own challenges in that regard.

10 Some of them are general, some of them are drug  
11 specific, and they may or may not be perfect  
12 solutions, but what we are doing is welcoming the data  
13 to help us clarify that.

14 Jay?

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

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

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

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

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

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

22                   DR. COHN: Well, I think it will depend

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

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

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

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

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

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

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

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

9 CHAIRMAN PACKER: Yes, please.

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

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

16 CHAIRMAN PACKER: Is that part of safety?

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

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

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

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

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

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1 status.

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

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

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

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

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

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

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

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

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

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

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

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

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

14 Then I showed you the results from study  
15 325 during the initial six hour period where diuretics  
16 were being withheld. We, again, did see a dose  
17 related increase in diuresis with Natrecor.

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

22 DR. MOYE: Excuse me, just one second.

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1 Those are very small numbers to draw such sweeping  
2 conclusions from. I mean, you have ends of less than  
3 30, in some cases less than 25. And for what they are  
4 worth, the P values here are kind of high.

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

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

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

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

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

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1 Jay?

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

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

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

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

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

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

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

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

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

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

4 DR. ALLGREN: I don't have a slide of  
5 that.

6 DR. ABRAHAM: I could actually share some  
7 data from protocol 306 if you would like, and I --

8 DR. GROSSBAR: We are not making a claim  
9 that the drug is clinically a diuretic. The data are  
10 confusing, they are certainly not overwhelming, they  
11 can't replace the use of ordinary diuretics in the  
12 management of heart failure.

13 We have followed this over several  
14 studies, sometimes there is some effect, sometimes  
15 there is less of an effect.

16 Most people who treat heart failure would  
17 not think it was a substantial effect, and so we've  
18 observed it, reported it, but we do not claim that  
19 this is a diuretic.

20 DR. COHN: Are you at all uncomfortable  
21 with the name of the drug, Elliott?

22 DR. GROSSBAR: We didn't name it. It is

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1 B-type natriuretic peptide, it is not our name. We got  
2 rid of the brain, that is a step forward.

3 DR. ABRAHAM: Well, I think in large part  
4 Elliott took the words out of my mouth, but I do think  
5 what the drug may suffer most from in the long term is  
6 its name. This class, in general, the natriuretic  
7 peptides, and as many of you know the effects of  
8 natriuretic peptides on the kidney has been a major  
9 focus of my own research.

10 And, basically, what we've shown is the  
11 response is very heterogenous. This is why the data  
12 looks as it does. In fact there are responders, and  
13 there are non-responders.

14 And what we have been able to best  
15 correlate with the renal response to natriuretic  
16 peptide is distal tubular sodium delivery. That is,  
17 if you are not delivering sodium to the site of action  
18 of a natriuretic peptide, you don't get natriuresis.  
19 And if you deliver it there you do.

20 And it is a highly variable response among  
21 heart failure patients. But I would agree with the  
22 company's position, this should not be marketed as a

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1       naturietic or diuretic agent.

2                   CHAIRMAN PACKER:   Ileana?

3                   DR. PIÑA:   You just made a statement that  
4       confused me.   You said diuretic use was stable, not  
5       changed.   I thought during the first six hours of 325  
6       there were no diuretics administered?

7                   DR. ALLGREN:   Right, right, right.

8                   DR. PIÑA:   Do you have any thoughts as to  
9       whether the improvement that you see here, in urine  
10      output during the first six hours could be related to  
11      an improvement in cardiac index as opposed to a  
12      variable effect on the kidney?

13                  DR. ALLGREN:   That is possible.   We just  
14      measured the urine output during that period, we  
15      didn't directly asses the mechanism of it.

16                  CHAIRMAN PACKER:   Does anyone have any  
17      other questions about efficacy?   One brief question.  
18      There was a change in either formulation or synthesis  
19      of the drug to a recombinant form.   Is that correct?

20                  DR. ALLGREN:   Pardon me?

21                  CHAIRMAN PACKER:   Is that correct?

22                  DR. ALLGREN:   Yes, the early studies ere

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1 done with drug made by synthetic methodology, and the  
2 later studies, and the commercial product will be a  
3 drug made by recombinant DNA the company. Both have  
4 the identical amino acid sequence to the endogenous  
5 BNP molecule.

6 CHAIRMAN PACKER: And the FDA reviewer  
7 made note of the fact that about 50 percent of the  
8 patients in the clinical trials got the first type,  
9 and fifty percent -- this is approximately -- got the  
10 second type.

11 Is the FDA, are the FDA reviewers  
12 comfortable that the difference between these two is  
13 not an issue to the committee?

14 DR. LIPICKY: Yes.

15 CHAIRMAN PACKER: Good. Let us take a ten  
16 minute break.

17 (Whereupon, the above-entitled matter  
18 went off the record at 11:30 a.m. and  
19 went back on the record at 11:42 a.m.)

20 CHAIRMAN PACKER: If we can have everyone  
21 take their seats, and we will proceed to the safety  
22 presentation.

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1 DR. HORTON: Thank you, Dr. Packer. Good  
2 afternoon.

3 In this safety summary today I will show  
4 you that the safety data from the Natrecor NDA support  
5 the use of Natrecor for short term treatment of  
6 congestive heart failure.

7 I will first review the clinical  
8 characteristics of the patients enrolled in the  
9 studies to show you that they well represent the  
10 target population for which Natrecor would be used.

11 I will then show you that there is no  
12 evidence for an increase in mortality with Natrecor  
13 use, then I will generally review the adverse event  
14 profile to show that Natrecor generally was well  
15 tolerated, and that the adverse event profile is very  
16 well characterized.

17 Finally I will show you data about  
18 outcomes after discontinuation of Natrecor to show  
19 that there is no evidence for an increase in the need  
20 for hospital readmission.

21 Let me begin by reviewing the safety data  
22 base.

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1           A total of 787 patients have received  
2 Nesiritide in clinical studies. These come from  
3 pharmacology studies in the literature, from a small  
4 study of Natreacor for another indication, and from the  
5 505 patients who received Natreacor in the Natreacor CHF  
6 program.

7           Of these 505 patients who received  
8 Natreacor in the NDA for CHF 111 of them received  
9 Natreacor as either a single IV bolus, or multiple IV  
10 boluses for less than 24 hours.

11           Of patients who received Natreacor as a  
12 continuous infusion, which is the recommended dosing  
13 regimen for Natreacor, the majority of those patients  
14 received Natreacor for more than 24 hours, with the  
15 bulk of them receiving Natreacor for 24 to 72 hours.

16           Many patients also received Natreacor for  
17 more than 72 hours, and the longest duration to date  
18 is 9 days.

19           To review the demographics, a total of 721  
20 patients were enrolled in the clinical studies, in  
21 eight clinical studies. The mean age was  
22 approximately 60 years, and about a third of the

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1 patients were more than 65 years of age. Women  
2 represented approximately 30 percent of the data base.

3 All patients in the Natreacor CHF program  
4 had chronic congestive heart failure. And as you can  
5 see here, most of them had neo heart association class  
6 III and IV.

7 In the two larger studies, study 325 and  
8 326, which Dr. Allgren already described to you, we  
9 also collected information about the patient's  
10 baseline medical and cardiac histories. These were  
11 typical CHF patients with a variety of co-morbidities,  
12 as you can see here, with a high percentage of  
13 patients having a history of hypotension prior to  
14 entry into the study, a history of a previous  
15 myocardial infarction, diabetes, and about 30 percent,  
16 or about a third, had chronic renal insufficiency.

17 It is important to note that a history of  
18 arrhythmias also did not exclude patients from  
19 participation in the studies. And, again, you can see  
20 that many of these patients had arrhythmias such as  
21 atrial fibrillation, frequent PVCs, and ventricular  
22 tachycardia.

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1 I'd like to also add to put a little more  
2 perspective to the patients that were enrolled in the  
3 325 study, that another indication of the level of  
4 decompensation for these patients is, for example,  
5 their baseline norepinephrine levels, which in study  
6 325 was a mean of 700 with normal being below 300.  
7 And the range of these values ranged from 200 to  
8 1,800.

9 In addition we had, of course, baseline  
10 BNP levels themselves, which correlate with a  
11 diagnosis of heart failure, and a BNP level greater  
12 than 50 picograms per milliliter is the cut-off for  
13 the diagnosis of chronic heart failure.

14 And the mean level of baseline BNP was  
15 1,500 in the patients in 325 at baseline.

16 Also as Dr. Allgren pointed out, those  
17 patients could have been hospitalized before entry  
18 into the study, and in fact, the range of time the  
19 patients were hospitalized was actually -- I'm sorry,  
20 up to 70 days.

21 Overall within the entire Natreacor NDA  
22 program we -- many patients were administered other

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1 commonly used cardiac medications, and this slide  
2 simply reflects the number of patients in the program  
3 that received these medications.

4 As Dr. Abraham pointed out, in one of the  
5 backup slides, study 326, which was the large safety  
6 study is really the best study to look at the  
7 medications that patients were on as they entered the  
8 study, and then whether those medications were  
9 continued during Natrecor therapy.

10 And I will just reiterate that more than  
11 60 percent of those patients were on Digoxin and ace  
12 inhibitors prior to entering into the study, and  
13 greater than 60 percent of the patients those  
14 medications were continued during Natrecor therapy.

15 So these data, again, support the fact  
16 that the experiences that occurred during the Natrecor  
17 program reflect the experiences that might be expected  
18 when the drug is used in usual clinical practice.

19 Now I would like to proceed to our data on  
20 mortality. These graphs show mortality rates with 95  
21 percent confidence intervals. The bars on the left  
22 reflect the mortality rates from the six studies that

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1 were placebo controlled only.

2 The blue bars represent placebo, the  
3 yellow bars represent Natrecor. In all of these  
4 studies patients were studied for two weeks, so we are  
5 representing 15 day mortality.

6 As you can see there is no evidence for an  
7 increase in mortality with Natrecor therapy when  
8 compared to control of placebo.

9 Now, the bars on the right reflect the  
10 mortality rates from the three largest studies, study  
11 311, 325, and 326.

12 Here I'm referring to these studies as the  
13 long infusion studies, because these are the studies  
14 in which patients received Natrecor generally for at  
15 least 24 hours. I would just like to remind you that  
16 the grey bar here, which is marked as control, is  
17 mostly comprised of patients who were receiving  
18 another IV vasoactive agent.

19 Again, those patients were followed for  
20 three weeks, so we are showing 21 day mortality. And,  
21 as you can see, there is no evidence for an increase  
22 in mortality with Natrecor therapy compared to

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1 control.

2 So in summary when compared to either  
3 placebo or active control there is no evidence for an  
4 increase in mortality with Natrecor therapy.

5 Allow me to move on to our data about the  
6 adverse event profile of Natrecor. First I will  
7 review the general adverse events which occur during  
8 the studies, and then I would like to spend a little  
9 more detail discussing the effects of Natrecor on  
10 blood pressure, heart rate, and serum creatinine.

11 This table shows all adverse events that  
12 were consistently reported more frequently with  
13 Natrecor therapy than control in all of the CHF  
14 studies.

15 As you can see here, symptomatic  
16 hypotension is the most frequently reported adverse  
17 event, followed by nausea, bradycardia in these other  
18 events are infrequently reported.

19 I would now like to show you these same  
20 events in the long infusion population so that you can  
21 see how these events relate to the doses of Natrecor  
22 that were administered in the pivotal studies.

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1           From this table you can see that the only  
2       adverse event, which is clearly dose related, is  
3       symptomatic hypotension.

4           I would like to focus our attention, for  
5       the next few minutes, on the effects of Natreacor on  
6       blood pressure. Generally speaking an infusion of  
7       Natreacor causes dose related decreases in blood  
8       pressure. This is reflected here with this graph,  
9       which shows the mean percent change in systolic blood  
10      pressure over the first six hours of infusion.

11          The blue line here is placebo from the 325  
12      study. The .015 dose reflected in yellow, and the .03  
13      dose reflected in green show a clear dose related  
14      response to blood pressure.

15          Now, to understand the greatest impact on  
16      blood pressure for all patients in the long infusion  
17      studies, the next slide summarizes the minimum  
18      systolic blood pressure that was observed at any time  
19      during the first 24 hours of therapy.

20          Please allow us to focus on the top rows  
21      first. The top row shows the median baseline systolic  
22      blood pressure, and the range, followed by the maximum

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1 decrease in systolic blood pressure in the treatment  
2 groups, and its corresponding minimum systolic blood  
3 pressure.

4 There is a couple of important points that  
5 I would like to share with you. One, you can see that  
6 the range is approximately 115, actually there were  
7 patients whose baseline systolic blood pressures were  
8 as low as 80 millimeters of mercury.

9 Secondly you can also see that all  
10 treatment groups experienced a drop in blood pressure,  
11 and I will just remind you that most of these control  
12 patients were on an inotrope.

13 Now, the bottom part of the slide shows  
14 each subject's minimum systolic blood pressure within  
15 the ranges shown here.

16 A couple of points here I would like to  
17 point out. First, it does appear, again, that the  
18 effect on Natrecor is dose related when you look at  
19 the numbers of patients who fall within different  
20 blood pressure ranges.

21 And, again, let me just emphasize that  
22 this is the minimum systolic blood pressure that was

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1 ever observed within the first 24 hours.

2 The other point I would like to make is  
3 that .015 is our recommended dose, and you can see  
4 here that two thirds of the patients who received the  
5 .015 dose maintained the blood pressure above 90  
6 millimeters of mercury at all times during the first  
7 24 hours.

8 So, in sum, these data support the fact  
9 that there is a dose related response of Natreacor on  
10 blood pressure, but that patients with decompensated  
11 heart failure experienced broad variations in blood  
12 pressure regardless of treatment.

13 Now, I would like to focus on symptomatic  
14 hypotension only, and how it impacted clinical  
15 management. And this slide shows the greatest impact  
16 that symptomatic hypotension had on the dosing of  
17 Natreacor.

18 What you can see here is in the .015 dose  
19 half of the patients that experienced symptomatic  
20 hypotension had that managed with either no change in  
21 the Natreacor dose, or a dose decrease. And the other  
22 half ultimately resulted in a discontinuation of

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1 Natrecor.

2 In the .03 dose there were more patients  
3 who experienced symptomatic hypotension, and more of  
4 these cases ultimately resulted in discontinuation of  
5 Natrecor.

6 Now, we further investigated whether  
7 symptomatic hypotension leads to serious adverse  
8 sequelae. In these complicated patients the  
9 relationship of an adverse outcome is particularly  
10 difficult.

11 The next slide shows a schematic  
12 summarizing the outcomes of all patients who  
13 experience symptomatic hypotension at any time during  
14 Natrecor therapy or within five hours after the  
15 discontinuation of Natrecor.

16 Now, in these three studies there were 336  
17 patients, if I could just walk you through this, this  
18 is not in your briefing document. There were 336  
19 patients enrolled in this study, 44 of those patients  
20 experienced symptomatic hypotension during this time  
21 frame, that is during study drug or within five hours  
22 after discontinuation of Natrecor.

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1                   292 of these patients did not ever have  
2 symptomatic hypotension. Of those patients with  
3 symptomatic hypotension 35 of them required no  
4 intervention, and here that is defined as the  
5 administration of an inotrope oppressor.

6                   And 9 of those patients did require  
7 administration of an inotrope oppressor. Of the 35  
8 patients who had symptomatic hypotension and required  
9 no intervention, 32 of these patients had no sequelae.

10                   Over here for the patients that had the  
11 administration of Dobutamine or Dopamine 5 of them had  
12 no sequelae. That leaves 7 patients, three from here,  
13 4 from here, that had subsequent events that might be  
14 felt to be related to symptomatic hypotension.

15                   Now I've divided this up into the two  
16 doses, and what you can see is that overall there were  
17 two patients in the .015 group that had symptomatic  
18 hypotension at some time during the study, and later  
19 died. And there were 7 patients in the .03 group that  
20 had symptomatic hypotension and later either died or  
21 had myocardial infarction, or dialysis.

22                   Now, in order to help you determine

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1 whether these 7 outcomes are related to symptomatic  
2 hypotension I'd like to briefly describe what happened  
3 with each of these patients, if you will just give me  
4 your attention for a few minutes here.

5 Real quickly. In the .015 dose the first  
6 patient was an 80 year old man who had not responded  
7 to seven days of Dobutamine therapy, and the  
8 Dobutamine was discontinued prior to entry into study  
9 325.

10 After six hours Dobutamine was resumed.  
11 Natrecor was continued until day three. This man was  
12 later made DNR within the next couple of days, and he  
13 died on day five.

14 The next patient is a 64 year old man who  
15 had Dobutamine added to Natrecor therapy after 24  
16 hours, for further inotropic support. Digoxin was  
17 initiated on day 2 after his second dose of Digoxin he  
18 developed second degree avery block and hypotension,  
19 which resolved with Atropine, a pacer wire, Digibind,  
20 and discontinuation of Natrecor.

21 This man later related to the investigator  
22 that he had had a similar episode months previous to

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1 that, and that was the reason why he wasn't on  
2 Digoxin.

3 His subsequent course include inotrope  
4 dependence, and a cardiac arrest. The patient  
5 requested discontinuation of all therapies, and he  
6 died on day four.

7 In the .03 dose there was a 77 year old  
8 woman with a hypertensive cardiomyopathy, who had a  
9 decrease in her systolic blood pressure from a  
10 baseline of 170 to 73 during Natrecor therapy.

11 The next morning routine cardiac enzymes  
12 were elevated. In retrospect, due to an elevated  
13 myoglobin upon admission, the investigator felt that  
14 the patient had an evolving myocardial infarction at  
15 study entry. This patient remained stable without  
16 symptoms, and was discharged.

17 The next patient, a 51 year old woman who  
18 had been hospitalized for one month for treatment of  
19 asthma, heart failure, and renal insufficiency was  
20 then enrolled into the study after one month of  
21 hospitalization.

22 Natrecor was administered and discontinued

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1 after 24 hours for refractory heart failure, with  
2 subsequent trials of Milrinone, Dopamine and  
3 Dobutamine.

4 A repeat trial of Natreacor was also  
5 unsuccessful, and on day 5 she was started on  
6 dialysis, and this patient remained on Dobutamine  
7 through the end of the study period.

8 The third patient in the .032 group, a 72  
9 year old woman had a recent aortic valve replacement  
10 and was still on a ventilator at the time of entry  
11 into the study. She received Natreacor for five days,  
12 she had a complicated course, and on day 13 developed  
13 renal failure requiring dialysis, she was discharged  
14 to home with a tracheostomy.

15 CHAIRMAN PACKER: Can we go through this  
16 a little bit more in less detail, please?

17 DR. HORTON: Sure.

18 CHAIRMAN PACKER: Case testimonies are not  
19 particularly very useful.

20 DR. HORTON: Yes. Actually, that is  
21 really the point that I would like to make, thank you  
22 for reminding me.

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1                   Because these patient narratives  
2 illustrate the difficulty of interpreting the  
3 relationship of hypertension that occurs with  
4 Natrecor, with any other drug, to subsequent events.

5                   And I certainly cannot make that  
6 determination. In this severely compromised  
7 population bad outcomes will occur. However, if  
8 symptomatic hypotension, which does occur more  
9 frequently with Natrecor therapy leads to more  
10 frequent adverse outcomes, then the relationship would  
11 be apparent in comparative data.

12                   So I would like to just bring up the next  
13 slide, which shows the frequency of these same events  
14 that are generally felt to be related to -- that may  
15 be related to symptomatic hypotension.

16                   DR. KONSTAM: I'm sorry to interrupt.

17                   DR. HORTON: Yes?

18                   DR. KONSTAM: I actually would like to  
19 hear about those two deaths.

20                   DR. HORTON: Okay. He is paying  
21 attention.

22                   Real quick. A 69 year old man with a

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1 history of multiple vascular surgeries and had a  
2 cardiac cath on the day of entry into the study. On  
3 day two he developed a femoral thrombosis, requiring  
4 surgical thrombectomy. Post-operatively he never  
5 regained consciousness, he was made DNR and he died.

6 Lastly a 61 year old man received Natreacor  
7 for five days, he deteriorated on day 5 after Natreacor  
8 was discontinued, and received Dobutamine and  
9 Dopamine, but died on day six.

10 DR. KONSTAM: Thank you.

11 DR. HORTON: Okay.

12 DR. LIPICKY: We actually make people do  
13 that, because some people like to agonize, apparently  
14 Marv likes to agonize.

15 DR. HORTON: I think the usefulness, if  
16 there is any at all, in describing those narratives,  
17 is to shed a little bit more light on the complicated  
18 nature of the patients that have been enrolled in the  
19 Natreacor program, which is consistent with the fact  
20 that the protocols have been extremely non-  
21 restrictive, and that we attempted to enroll typical  
22 heart failure patients.

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1                   SO this slide here shows the frequency of  
2                   those same events, in the three larger studies, 311,  
3                   325 and 326, within the 21 day study period. And you  
4                   can see that there is no evidence for an increase of  
5                   these events with Natrecor therapy than control.

6                   Now I would like to focus our attention to  
7                   the changes in heart rate that occur with Natrecor  
8                   therapy. Although Natrecor is an effective  
9                   vasodilator, it has not been associated with an  
10                  increase in heart rate.

11                  This may contribute to the decrease --  
12                  this does contribute to the decrease in rate pressure  
13                  product, which is observed during Natrecor therapy,  
14                  suggesting that maybe there is a reduction in  
15                  myocardial oxygen consumption.

16                  Bradycardia was also reported, occurring  
17                  in four percent of patients in the .015 group, and 5  
18                  percent of patients in the .03 group. Mechanistically  
19                  I would like to point out that Natrecor is not  
20                  associated with AV node conduction abnormalities.  
21                  These episodes of bradycardia generally have been  
22                  sinus bradycardia with rare episodes of junctional

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1 bradycardia.

2 This next slide summarizes the clinical  
3 significance of bradycardia. Bradycardia that was  
4 reported in the .015 dose was described as mild or  
5 moderate in all cases. It usually resolved  
6 spontaneously within one to fifteen minutes.

7 And as you can see, from this slide, in  
8 only one case did it result in a discontinuation of  
9 Natreacor.

10 In fact, in this case, the patient also  
11 had decreases in blood pressure, which also led to the  
12 discontinuation of the drug.

13 Since the .03 dose generally is associated  
14 with larger decreases in blood pressure than the .015  
15 dose, bradycardia occurring in this dose is also more  
16 likely to occur with hypotension and to result in the  
17 discontinuation of Natreacor.

18 There has not been a case, in the .015  
19 group where Atropine has been administered, but there  
20 has been one in which a patient developed a junctional  
21 bradycardia, and was administered Atropine in the .03  
22 dose.

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1 I would also like to just point out that  
2 there have been no serious adverse sequelae related to  
3 Natrecor induced bradycardia to date. The last  
4 specific phenomenon, which I would like to describe in  
5 more detail is the effect of Natrecor on serum  
6 creatinine.

7 I'm only focusing on this laboratory value  
8 because there are no other clinically significant  
9 laboratory changes with Natrecor therapy.

10 In addition serum creatinine is commonly  
11 affected by the disease process, itself, as well as by  
12 other acute therapies.

13 This slide shows us the baseline  
14 creatinine values, and I will just reiterate that  
15 there was, at least in 325 and 326, no restriction on  
16 the level of creatinine for patients who could be  
17 included in the study.

18 But at the last available value, overall,  
19 there is no change in creatinine, in the change of  
20 creatinine from baseline.

21 However, we looked for subsets of patients who  
22 might had clinically relevant increases in creatinine,

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1 and for this analysis we've defined that as a  
2 creatinine greater or equal to two, and at least 50  
3 percent increased.

4 When we did we found that 6 and 10 percent  
5 of Natrecor patients had this elevation in creatinine,  
6 whereas only 2 percent of the control patients had  
7 this elevation creatinine meeting this criteria.

8 Generally these increases in creatinine  
9 were transient, and returned to baseline, or near  
10 baseline within a couple of days to a few weeks.

11 Information about each of these patients  
12 was provided to you in detail in the briefing  
13 document, but I would just like to show you the  
14 follow-up values for the patients in the .015 group,  
15 specifically.

16 So this slide shows you, generally, that  
17 there is a pattern of creatinine returning to  
18 baseline, or near baseline. I would like to point out  
19 that there were also many other reasons why creatinine  
20 might have been increased in these patients.

21 For example this patient here with the  
22 orange line is a patient who had a bladder outlet

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1 obstruction and the creatinine resolved with placement  
2 of a foley catheter.

3 More importantly, when we looked at  
4 patients who had even more clinically significant  
5 increases, or effects on renal function, as  
6 represented by either an increase in creatinine of  
7 more than 100 percent, or patients who developed acute  
8 renal failure requiring dialysis, you can see from  
9 this slide that there is no difference in the  
10 frequency of these events compared to control.

11 So, in summary, Natrecor may lead to mild  
12 to moderate rises in serum creatinine but do not lead  
13 to adverse sequelae, necessarily. These changes in  
14 creatinine are biochemical changes, and not  
15 significant adverse experiences in most patients.

16 In addition we do not believe that this is  
17 due to a direct toxic effect of Natrecor on the  
18 kidneys, because in multiple toxicology studies,  
19 including a two week toxicology study in monkeys,  
20 there has been no evidence for any laboratory or  
21 histologic evidence of renal toxicity.

22 So to put these events in the context of

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1       how they might compare to the safety profile of other  
2       agents for this indication, the prospective safety  
3       study, study 326, provides us this opportunity.

4               This was the largest study, enrolling 305  
5       patients with decompensated heart failure requiring  
6       hospitalization and IV vasoactive therapy. There was  
7       no ejection fraction requirement for this study.

8               This was an active control study where,  
9       again, the control patients received an IV vasoactive  
10      therapy of the investigator's choice. No central  
11      hemodynamics were measured, and there was no  
12      requirement for a PA line. And that decision was left  
13      to the discretion of the investigator.

14              This study also allows us to understand  
15      the adverse event profile when Natrecor is  
16      administered for longer than 24 hours, since the  
17      median duration of study drug was 43 to 67 hours in  
18      the different groups.

19              The next slide summarizes the events that  
20      I have already mentioned. But here the frequency of  
21      these events, occurring during the entire duration,  
22      are shown.

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1           In this study, where 102 patients were  
2 randomized to control, 58 of them received Dobutamine,  
3 19 received Milrinone, 18 received nitroglycerin.  
4 There were 6 others who received either Dopamine or  
5 Amiodarone, and there were not enough to summarize  
6 with this type of an analysis.

7           Whereas symptomatic hypotension overall  
8 was more common in the Natrecor groups compared to  
9 control, when you look at the frequency of these  
10 events for specific agents, the frequency of  
11 symptomatic hypotension with Milrinone was not  
12 different from that of the .015 dose of Natrecor. It  
13 was also not uncommon with Dobutamine.

14           The adverse event of increased creatinine  
15 was similar to that reported in the Natrecor groups.  
16 Nausea was frequently reported with both Dobutamine as  
17 well as with nitroglycerin.

18           In conclusion the adverse events that may  
19 be associated with Natrecor therapy are also events  
20 which are not uncommon with other currently available  
21 agents.

22           In addition, these particular events

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1 should be easily managed in a clinical setting, in  
2 which vital signs in serum creatinine are routine.

3 Now, up until now I've been focusing on  
4 events that have been more common with Natrecor  
5 therapy than control, but it is important to note that  
6 there were certain events that were less frequently  
7 reported with Natrecor therapy.

8 For example, again, in our safety study,  
9 study 326, there were three percent of the control  
10 patients experienced a cardiac arrest at some time  
11 during study drug infusion, whereas no Natrecor  
12 patient had a cardiac arrest during study infusion.

13 It turns out that all of those patients  
14 were Dobutamine patients. Sustained ventricular  
15 tachycardia was more common in the control group than  
16 Natrecor, and those events generally occurred with  
17 Dobutamine, as well.

18 Ventricular extrasystole was also less  
19 frequent with Natrecor, and mostly those were reported  
20 with Milrinone therapy. Finally, headache was most  
21 common with nitroglycerin therapy and was not uncommon  
22 with the other therapies, but generally reported less

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1 frequently with Natreacor than the other therapies.

2 So when looked at in the context of how  
3 Natreacor's adverse event profile may compare to agents  
4 which are currently available, there may in fact be  
5 some safety advantages of Natreacor over these agents.

6 Now I would like to briefly summarize the  
7 effect of Natreacor on outcomes related to safety that  
8 were collected through the 21 day study periods.

9 In these studies we prospectively  
10 collected whether there was a need for emergent  
11 intubation and readmissions, we also collected length  
12 of stay. You can see here that there is no evidence  
13 for an increase in the need for emergent re-  
14 intubation, or a difference in length of stay with  
15 Natreacor compared to control.

16 We prospectively collected whether  
17 readmissions occurred, and whether they were for all  
18 causes, or for recurrent CHF, specifically. And,  
19 again, you can see here that there is no evidence for  
20 an increased need for hospital readmission in Natreacor  
21 versus control within the 21 day study period.

22 Together these data suggest that there is

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1 no evidence for an increased need for medical  
2 interventions, generally, after Natrecor is  
3 discontinued.

4 In summary I have demonstrated that the  
5 safety data from the Natrecor NDA support the use of  
6 Natrecor for the short term treatment of congestive  
7 heart failure. I've shown you that the safety data  
8 base well represents the target population that would  
9 receive Natrecor for this indication.

10 Generally that Natrecor is well tolerated,  
11 and that the safety profile for Natrecor has been very  
12 well characterized. Finally I've showed you that  
13 there was no evidence for an increase in mortality or  
14 for the need of hospital readmissions.

15 Thank you for your attention, I would be  
16 happy to answer any questions you might have.

17 CHAIRMAN PACKER: Why don't we go onto the  
18 next presentation, and we will take questions for  
19 both, in the interest of time.

20 DR. HORTON: Okay. I would like to  
21 introduce Dr. Abraham from the University of  
22 Cincinnati, who will discuss the benefit risk

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1 assessment of Natrecor.

2 Thank you.

3 DR. ABRAHAM: thanks very much. Dr.  
4 Packer, Committee members, Dr. Cohn, members of the  
5 FDA staff, it is my pleasure to offer a clinician's  
6 view of the benefit risk assessment of Natrecor for  
7 the short term intravenous treatment of decompensated  
8 heart failure.

9 As a heart failure specialist and clinical  
10 investigator, I have substantial first-hand experience  
11 with the use of Natrecor in such patients. This  
12 begins with my involvement in one of the first human  
13 studies of Natrecor and heart failure protocol 306,  
14 and includes my participation in the two pivotal  
15 efficacy studies reviewed today.

16 Based on this experience, as well as an  
17 understanding of the data presented today I'm quite  
18 enthusiastic about the benefit risk assessment for  
19 this drug.

20 I would like to begin with a brief review  
21 of the current status of acute heart failure. This  
22 will be followed by a summary of the demonstrated

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1 benefits of Natrecor. I will then reiterate some of  
2 the clinically important risks of Natrecor therapy in  
3 decompensated heart failure, and before concluding I  
4 would like to describe candidates for treatment with  
5 this agent, and I will try to do all of this in about  
6 ten minutes.

7 This slide lists the current status of  
8 acute heart failure. I think as you all appreciate  
9 decompensated heart failure represents a major public  
10 health concern, in that it accounts for nearly one  
11 million hospitalizations annually in the United  
12 States, as well as substantial morbidity and  
13 mortality.

14 While current therapies are generally  
15 effective, they may be limited by adverse events, such  
16 as the risk for life threatening arrhythmias seen with  
17 the positive inotropic agents.

18 Thus I believe that there is a need for  
19 alternative therapies for decompensated heart failure.  
20 In this regard it is worth noting, as noted earlier,  
21 that no new intravenous drugs for the treatment of  
22 decompensated heart failure have emerged for

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1 consideration by this Advisory Panel in more than a  
2 decade.

3 Given all of this another option for  
4 therapy is warranted. This slide lists the  
5 demonstrated clinical benefits of Natrecor in  
6 decompensated heart failure. In sum, Natrecor  
7 produces significant dose related favorable effects on  
8 hemodynamics while improving patient symptoms.

9 Specifically Natrecor significantly  
10 improves hemodynamics by decreasing pulmonary  
11 capillary wedge pressure and systemic vascular  
12 resistance.

13 In this regard Natrecor is a balanced  
14 vasodilator. Natrecor significantly increases cardiac  
15 output by improving stroke volume, not by increasing  
16 heart rate with no direct inotropic effect.

17 Finally, Natrecor produces rapid symptom  
18 improvement during therapy, as ascertained by patient  
19 and physician global clinical assessments, and by  
20 specific symptom scales.

21 In addition there are some ancillary  
22 benefits of Natrecor which support its use in heart

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1 failure. For example, Natreacor has a generally  
2 favorable neurohormonal profile in that it reduces  
3 plasma aldosterone, and maintains or reduces plasma  
4 norepinephrine.

5 The clinically relevant risks of Natreacor  
6 have just been extensively reviewed by Dr. Horton, and  
7 are reiterated on this slide. Natreacor produces dose  
8 related hypotension, which may be viewed as excessive  
9 pharmacologic effect.

10 In this regard the effect of Natreacor to  
11 produce hypotension is similar to that seen with other  
12 vasodilators used for the treatment of heart failure.

13 Bradycardia occurred uncommonly, in less  
14 than or equal to 5 percent of subjects. And as you  
15 have seen there were no untoward sequelae associated  
16 with the incidence of bradycardia.

17 Finally, six to ten percent of patients  
18 experienced an increase in serum creatinine defined by  
19 an increase of at least 50 percent to a value of at  
20 least 2 milligrams per deciliter associated with  
21 Natreacor therapy.

22 While these increases in serum creatinine

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1 are commonly seen during the treatment of  
2 decompensated heart failure, and have generally been  
3 attributed to peripheral vasodilation, and/or relative  
4 intravascular volume depletion, so called arterial  
5 underfilling, it is most important to note that  
6 clinically significant renal dysfunction, such as that  
7 requiring hemodialysis, was rare in the Natrecor  
8 group, and its incidence was not increased compared to  
9 the control arms of these studies.

10 Now, these demonstrated risks of Natrecor  
11 are certainly concerning to the clinician. But I  
12 would suggest that these adverse events are  
13 predictable, they are manageable, and as you have seen  
14 they do not produce adverse outcomes that are  
15 dissimilar, or occurred in increased frequency  
16 compared to standard or currently available forms of  
17 therapy for decompensated heart failure.

18 This slide presents a simplified view of  
19 a rational approach to therapy in volume overloaded  
20 heart failure patients. And I present this to you not  
21 because I'm naive and don't believe that you already  
22 understand how to treat decompensated heart failure,

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1 but really to demonstrate a couple of points regarding  
2 what I believe is the over utilization of inotropes,  
3 and under utilization of IV vasodilators in  
4 contemporary heart failure management.

5 Here you can see that patients presenting  
6 with clinical congestion may be categorized into one  
7 of three groups based on an assessment of peripheral  
8 perfusion.

9 Patients with adequate perfusion are often  
10 well treated with diuretics, plus oral or intravenous  
11 vasodilators. Patients with frank cardiogenic shock  
12 require intravenous pressor agents to support blood  
13 pressure, in addition to diuretics for extra cellular  
14 fluid volume excess.

15 But this large group of patients in  
16 between, with clinical congestion, and reduced  
17 perfusion, may be treated with diuretics plus either  
18 an intravenous vasodilator, or intravenous inotrope.

19 Now, we have seen, in the control arms of  
20 these Natreacor studies, and we know from clinical  
21 pharmacy surveys, that most clinicians currently  
22 choose to use an intravenous inotrope in these group

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1 of patients, thus subjecting them to substantial  
2 risks, such as the risk of life threatening arrhythmia.

3 The apparent under-utilization of  
4 vasodilators in these patients may relate to the  
5 common perception that nitroglycerin is relatively  
6 ineffective, and that nitroprusside is difficult to  
7 use, thus there is a need for alternative or  
8 additional vasodilator therapy in these patients for  
9 drugs such as Natreacor.

10 In this regard candidates for treatment  
11 with Natreacor are hospitalized patients, with  
12 decompensated heart failure requiring intravenous  
13 vasoactive therapy. Specifically they should be  
14 volume overloaded, and not in cardiogenic shock.

15 This may represent the typical patient  
16 hospitalized for decompensated heart failure,  
17 according to numerous clinical benchmarking studies.

18 I believe this also represents the typical  
19 patient studied in this NDA with an average pulmonary  
20 capillary wedge pressure of about 25 or 30 millimeters  
21 of mercury, and an average cardiac index of around  
22 1.8.

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1           In addition there are other clinical  
2 considerations which you and I might consider in  
3 favoring Natreacor over other agents for the treatment  
4 of decompensated heart failure.

5           Given the known effects of Natreacor on  
6 heart rate, it may be particularly useful in  
7 tachycardiac patients where positive inotropic therapy  
8 is often limited.

9           Given the known vasodilatory effect of  
10 Natreacor, it may be preferred in patients with  
11 hypertensive heart failure, where vasodilators clearly  
12 have an established role.

13           And, finally, given the lack of a positive  
14 inotropic effect of this agent, it may be preferable,  
15 in those patients with a history of malignant  
16 ventricular arrhythmias, which may be exacerbated by  
17 positive inotropic agents.

18           In summary, Natreacor is a safe and  
19 effective form of intravenous therapy for patients  
20 with acutely decompensated heart failure. Natreacor  
21 has an excellent benefit risk profile, specially when  
22 viewed in the context of existing therapies.

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1 could get rid of hypotension rapidly, rapid on, rapid  
2 off.

3 And I guess I would like some handle on  
4 that. And in thinking about it, I don't think it  
5 comes, necessarily, from the patients who had  
6 hypotension as an adverse effect, because in those  
7 patients there probably were going to be other things  
8 going on to correct the hypotension, like volume  
9 replacement, or maybe even pressors.

10 So maybe the only handle on this comes  
11 from the overall population, and what happens to blood  
12 pressure when you turn off the drug.

13 And that was shown earlier, briefly. Do  
14 you want to show that again, in terms of the kinetics  
15 of the return of the blood pressure to normal after  
16 you turn off the drug?

17 DR. HORTON: I think that was actually, we  
18 only showed that for wedge pressure and cardiac index.  
19 I don't believe that we have --

20 DR. KONSTAM: I thought I saw something  
21 pop up, but if not I would like to see it for the  
22 first time.

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1 DR. HORTON: Actually we don't. I'm  
2 sorry, we don't have a graph showing the blood  
3 pressures returning to any particular level after the  
4 discontinuation of Natreacor in the overall population.

5 DR. KONSTAM: Well, you have to have that.  
6 I mean, this is going to be important.

7 DR. HORTON: We will get that information  
8 for you.

9 DR. KONSTAM: I thought that I saw a slide  
10 that had multiple panels on it, one of which was blood  
11 pressure, I thought it was in the top right-hand  
12 corner. Maybe I was --

13 DR. HORTON: There is a slide from study  
14 325 --

15 DR. KONSTAM: There was not any blood  
16 pressure on it?

17 DR. HORTON: There is a slide that shows  
18 the blood pressure effect, but it doesn't continue  
19 through after discontinuation of Natreacor.

20 CHAIRMAN PACKER: I think the slide you  
21 are referring to is one that goes to six hours. The  
22 one that you are asking about is at 311 with the four

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1 hour withdrawal period, at 24 hours, and we didn't see  
2 that, that was the only two variables that were put  
3 forward.

4 DR. HORTON: Right.

5 DR. KONSTAM: So I'll just editorialize  
6 again, that we are going to say, I mean, Bill made  
7 some points that this is going to be a useful agent,  
8 and in clinical practice that is going to be relevant  
9 to what.

10 And then the only way to get a handle on  
11 this hypotensive question is just this issue, how  
12 quickly will it go away when you stop the drug. At  
13 least that is how I'm going to evaluate it relative to  
14 other drugs, for what that is worth.

15 DR. HORTON: One thing I can add is that  
16 in the overall population, which is what you are  
17 asking, that at 24 hours in study 311 for example,  
18 which is the one where we do have some blood pressure  
19 information after discontinuation, the overall effect  
20 on blood pressure in that population, in the .015 dose  
21 and the .03 doses was between 5 and 10 millimeters of  
22 mercury.

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1                   And then after discontinuation of the drug  
2                   the blood pressures would have gone up a little bit.

3                   DR. KONSTAM:   Okay.

4                   DR. ABRAHAM:   I'm not sure that we have  
5                   the exact slide that you want, but I think it is a  
6                   reasonably safe presumption that it probably parallels  
7                   the same offset of effect that we see with wedge  
8                   pressure or SVR.

9                   DR. KONSTAM:   Okay, right.

10                  DR. ABRAHAM:   And you have seen those  
11                  slides before.

12                  But I think even more importantly than  
13                  that is the slide that Darlene showed looking at the  
14                  outcomes in these patients. I think we want to know  
15                  what happens on the short term, and how long does it  
16                  take for the blood pressure to come back, and how they  
17                  are treated.

18                  You know, the bottom line here is that you  
19                  can't really say that it produced adverse outcomes  
20                  looking at hard outcomes.

21                  DR. KONSTAM: I understand that point, and  
22                  they are two separate points, and I think it is -- we

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1 shouldn't get into outcomes quite yet. I'm just  
2 trying to get a handle on the blood pressure, the  
3 adverse effect of hypotension that we see, and what  
4 could be done.

5 I also would say, just commenting on the  
6 wedge pressure study. So if I'm not mistaken the  
7 return to normal and wedge pressure was hours, number  
8 one.

9 And number two is, it doesn't really help  
10 me all that much anyway, because wedge pressure is  
11 driven in part by intravascular volume shifts. And so  
12 that is not the same as blood pressure.

13 So I'm still left with that big question  
14 mark in my mind.

15 DR. HORTON: Dr. Konstam, I just also want  
16 to point out, unfortunately we only measured blood  
17 pressure two hours after discontinuation, and four  
18 hours after discontinuation.

19 So in the overall population I can only  
20 tell you those values. We have additional information  
21 about patients who had developed hypotension with  
22 repeated blood pressures in their resolution.

1           In one of the tables in the briefing  
2 document, under the hypotension section, for example,  
3 a third of the patients have their hypotension  
4 resolved within 30 minutes.

5           Unfortunately, for the benefit of the  
6 people in the audience I will just talk through this  
7 a little bit while the Committee is finding the table.

8           This is a summary of the duration of the  
9 event of symptomatic hypotension. Now, in some of  
10 these cases it was a single event, a transient event,  
11 as I said. In a third of the cases it resolved within  
12 a few minutes to 30 minutes.

13           This also includes, though, patients who  
14 had intermittent hypotension. So some of these cases  
15 did last for several hours. The entire duration of  
16 the event is several hours, although it was  
17 intermittent during that time.

18           CHAIRMAN PACKER: Marv, it is 65 in the  
19 briefing document.

20           DR. HORTON: Actually, could I have backup  
21 slide 311, please?

22           DR. RODEN: Are you going to tell us how

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1 many of these patients had bradycardia and hypotension  
2 at the same time?

3 DR. HORTON: There were two patients in  
4 the .015 group that had -- I'm sorry. Yes, there were  
5 two of these patients in the .015 group that had  
6 bradycardia, and seven patients in the .032 group that  
7 had bradycardia and hypotension.

8 DR. RODEN: Bradycardia and hypotension at  
9 the same time, okay.

10 DR. HORTON: Yes.

11 DR. KONSTAM: Right. And, again, so this  
12 useful. Again, the problem is there are other things  
13 going on. The responses to this is going on, so we  
14 don't know even what -- to what extent this represents  
15 the drug going away, and to what extent it is the  
16 responses to the hypotension going on.

17 DR. HORTON: Yes, that is true. This also  
18 includes those patients where there was no change in  
19 the Natreacor dose, the Natreacor was continued.

20 DR. ABRAHAM: In addition to confound the  
21 picture further, these patients were receiving  
22 standard medications for heart failure, so they may

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1 have received their long acting ace inhibitor just  
2 before their episode of hypotension, and so you really  
3 cannot discern the offset effect.

4 This is not a clinical pharmacology study.

5 DR. KONSTAM: So I'm back to where I  
6 started from, which is the only thing that I can think  
7 of that is really going to help me on this, is looking  
8 at some population data and stopping the drug, and  
9 seeing what happens to blood pressure in a controlled  
10 setting. That is really the only thing I can think of  
11 that is really going to help me.

12 DR. HORTON: I do have late breaking news  
13 on that point, from my competent colleagues in the  
14 second row.

15 In study 311, after 24 hours, patients in  
16 the .015 group had a mean decrease in blood pressure  
17 of minus six milliliters of mercury. The .03 group  
18 was minus 3.3. And in the .06 group, which is a dose  
19 we are not recommending, it was minus 9 dose related  
20 effect.

21 Two hours after discontinuation, the first  
22 time point that we measured it in the overall

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1 population, the results are plus 2 millimeters of  
2 mercury in the .015 group, so it is back to baseline;  
3 minus 3 in the .03 group, and minus 6 in the .06  
4 group; and then at 4 hours the numbers are zero, minus  
5 3, and minus 2.

6 So certainly within two hours the numbers  
7 are, the blood pressures are back to baseline. But  
8 that likely happened before that.

9 DR. KONSTAM: Well, I don't get that  
10 exactly. I mean, they got back to baseline in the  
11 .015 group, but not in the other groups, right?

12 DR. HORTON: That may be true, yes.

13 DR. KONSTAM: Okay. Can I ask about the  
14 creatinine question, one question I had. Do you have  
15 any information about relating creatinine to blood  
16 pressure effects? I don't know, can you get a handle  
17 to what extent it is being driven by blood pressure?

18 DR. HORTON: I do. Can I have backup  
19 slide 335, please?

20 Actually to answer two parts of this  
21 question, the first part of this slide looks at the  
22 risk of increased creatinine according to baseline

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1       systolic blood pressure.     And you can see that  
2       patients who have a baseline systolic blood pressure  
3       of less than 100, and there are 50 of those patients  
4       in the all Natrecor group, there is no increased risk  
5       for those patients of developing increased creatinine.  
6       That is one point.

7                 Secondly, if you look at patients who had  
8       a systolic blood pressure lower than 85 at any time  
9       during the first 24 hours, there again is no apparent  
10      increased risk.

11                DR. KONSTAM:   Okay.   Now, I have another  
12      question, which is plasma proteins, you didn't talk  
13      about that at all.   There is some evidence that I see  
14      in the data set that plasma protein levels are going  
15      down significantly in the treatment groups.

16                Do you want to comment about that?

17                DR. HORTON:   I'm sorry, I don't have that  
18      information in front of me.

19                In our analysis the minimal changes that  
20      were seen with plasma proteins were not clinically  
21      significant.   I don't really have any further comment.

22                DR. KONSTAM:   Well, in the medical

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1 reviewers -- in the Agency document on page 157 and  
2 158 there are tables related to decreases in total  
3 protein concentration. The table on the bottom of  
4 page 157 is the all heart failure trial, and on top of  
5 158 is the long infusion trials.

6 And in the Nesiritide group, for example,  
7 taking one piece of data, last available on or before  
8 day 2, I guess, control 14 percent, Nesiritide 34  
9 percent, P equals .001.

10 And then, similarly, taking the long -- I  
11 mean, that is just one piece of data, we can look at  
12 the whole table. Long infusion trials similar sort of  
13 data. Last available on or before day 2.

14 For example, in the Nesiritide .015 group,  
15 47 percent of the patients, compared to 13 percent of  
16 the controls, P equals .038.

17 So it seems like it is happening.

18 DR. HORTON: Right. Could I see backup  
19 slide 348, please?

20 You are referring to patients who, when  
21 you say 48 percent of the patients you are referring  
22 to --

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1 DR. KONSTAM: Well, I'm just reading from  
2 the table. I mean, somebody else can --

3 DR. HORTON: But it is 8 percent of  
4 patients that had a change from normal to low. What  
5 is it?

6 DR. KONSTAM: I don't know.

7 DR. HORTON: I think it is difficult --

8 DR. LIPICKY: You might ask the reviewer  
9 why he thought it was reasonable to calculate P values  
10 here.

11 DR. THROCKMORTON: I didn't do that.

12 DR. LIPICKY: Who did that?

13 DR. THROCKMORTON: The sponsor. Those  
14 were looking at -- those are shift table analyses  
15 looking at changes from normal value at baseline to,  
16 in this case, abnormally low serum protein values,  
17 either total protein or albumin.

18 And that is data that was prepared by the  
19 sponsor.

20 DR. LIPICKY: Do you know why you  
21 duplicated the P values, why did you record them?

22 AUDIENCE: Completeness sake.

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1 DR. LIPICKY: He did a very thorough  
2 review, right?

3 DR. HORTON: I will just bring your  
4 attention to the slide here, which actually talks  
5 about the magnitude of the changes that were seen in  
6 the two top labs are protein and albumin. And this is  
7 at the last available laboratory value representing  
8 the change from baseline, which is minus 0.1 in the  
9 three treatment groups.

10 DR. KONSTAM: I don't know, this is, you  
11 know, one of the points that was made by the medical  
12 reviewer. It did strike me as interesting,  
13 intriguing, and maybe of some potential concern  
14 relative to what the drug is doing.

15 And I guess the general question, I mean,  
16 maybe I can ask, you know, open it up in terms of the  
17 general mechanism with regard to the drug, whether  
18 there is an increase in vascular permeability, and an  
19 increase in third spacing going on.

20 DR. LIPICKY: You might ask Doug whether  
21 that is what he implied.

22 DR. KONSTAM: Doug, is that what you

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1 implied?

2 DR. THROCKMORTON: Yes, in fact that was  
3 the thing that I did raise. That is something that  
4 has been suggested in several papers for atrial  
5 natrietic peptide, and was in fact something that I  
6 thought was a possible mechanism for BNP as well.

7 CHAIRMAN PACKER: Do you have questions  
8 for Bill, as well?

9 DR. KONSTAM: I do. Bill, where are you?  
10 I can't see you. I enjoyed your presentation. I  
11 mean, I guess you made one comment nitroprusside is  
12 difficult to use. Why do you think nitroprusside is  
13 difficult to use?

14 DR. ABRAHAM: I think, and I want to be  
15 very carefully -- I wanted to state this very  
16 carefully. I think what I said was that nitroprusside  
17 is seen or perceived to be very difficult to use.

18 In fact, I readily use nitroprusside for  
19 the treatment of these patients. But it is  
20 interesting that if you look at the control arms of  
21 these Natrecor studies, nobody chose to use  
22 nitroprusside as the control agent.

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1           And I think that that is fairly reflective  
2 of common practice. But I would suggest that that may  
3 represent under-utilization of a good therapy.

4           DR. KONSTAM: Well, let me ask you the  
5 question. You identified patients in whom you would  
6 consider using Nesiritide. Can you tell me what is  
7 the patient profile that if you had in front of you  
8 right now you would prefer to use Nesiritide over  
9 nitroprusside?

10          DR. ABRAHAM: I think in general, with  
11 experience with both agents, that I would probably  
12 favor using Natrecor in the patients that I would  
13 consider for nitroprusside.

14           And the reason for that, and I want to be  
15 very careful about making comments which are evidence  
16 based and data driven, but I do believe that the  
17 overall profile of a naturietic peptide, in general,  
18 and of this agent in particular, has some effects  
19 which are desirable to go beyond strictly a  
20 vasodilator.

21           I think that there are favorable effects  
22 on neurohormonal profile, there clearly are favorable

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1 effects on heart rate and rate pressure product. And  
2 while we can debate and talk about responders and non-  
3 responders, there appears to be, in most patients, a  
4 generally favorable effect on the kidney.

5 Although we have seen in all circumstances  
6 where we treat heart failure we can also go the other  
7 way, and we can cause pre-renal acidemia and we can do  
8 that with this agent as well.

9 DR. KONSTAM: Well, I'm just commenting.  
10 I mean, I respect your conclusions, but I don't see  
11 any of them really being driven by the data set here.

12 I mean, am I missing something?

13 DR. ABRAHAM: Well, I think they are  
14 driven in part by this data set, but again I've taken  
15 a little liberty and also considering the general fund  
16 of knowledge surrounding the use of naturietic  
17 peptides in these patients.

18 DR. STEVENSON: I think the majority of  
19 the use of nitroprusside in the United States is  
20 represented within this auditorium here. I'm clearly  
21 a great proponent of it, as you know.

22 However, I've been increasingly distressed

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1 that our colleagues do not use it. There is  
2 considerable concern about Nipride toxicity due to  
3 cyanide. Whether or not it occurs as often as  
4 everybody worries about it, and I'm really distressed  
5 at the fact that inotropic therapy is beginning to  
6 really take over in most of our colleagues' practices,  
7 due to concerns that they cannot use nitroprusside,  
8 and I feel we really need an alternative.

9 CHAIRMAN PACKER: Dan?

10 DR. RODEN: Something you said reminded me  
11 of a question I wanted to ask. And that is, you  
12 attributed the effect of Nesiritide on natriuretic  
13 peptide action. And I want you, or somebody from the  
14 sponsor to speculate about what the mechanism of  
15 action of this compound really is.

16 You told me earlier that you didn't think  
17 it -- you thought it was a misnomer to call it a  
18 natriuretic peptide. So I would like some sense of  
19 what it does at the biochemical, or at the fundamental  
20 cellular level to achieve these actions.

21 And maybe you can -- you mentioned also  
22 that it had -- produces a favorable neurohormonal

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1 profile, but we didn't see any of those data, and I  
2 would like to see some sense of what it does to  
3 catecholamines, and other measures of neurohormonal  
4 status, if you have them.

5 DR. ABRAHAM: I believe we have some  
6 backup slides on neurohormonal profile, and perhaps  
7 while we locate this we can comment on mechanisms of  
8 action.

9 There are representatives from the  
10 sponsoring company here, that have done some of the  
11 basic cellular physiology with the compound, and I  
12 would invite them to come to the microphone, if they  
13 wish.

14 But basically this effect is mediated via  
15 cyclic GNP, as the intracellular second messenger.  
16 And so you would presume that the typical effects that  
17 cyclic GNP has, would be seen with this agent.

18 DR. PRATTER: Yes, I'm Dr. Andrew Pratter,  
19 and I've done the pre-clinical pharmacology for the  
20 program, for SCIOS, and we have studied in cells, and  
21 in animals, the mechanism of BNP.

22 And it is well known in terms of receptor

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1 mediated actions that it is interacting specifically  
2 in a high affinity manner with what is called the  
3 guanalose cyclase A, or the GCA particulate guanalose  
4 cyclase receptor.

5 That is very clear. Receptor knockout  
6 studies in which that receptor is specifically taken  
7 out of mice, they no longer vasodilate in response to  
8 BNP. And David Garber in Texas has shown this very  
9 nicely.

10 With regard to what it is doing in vivo,  
11 we know reproducibly, when you give this to an animal,  
12 that the vasculature, we get vasodilation. You can  
13 see reductions in systolic blood pressure, which is  
14 very consistent with the decrease in pre-load.

15 Before it was mentioned, the issue of  
16 blood volume, and whether you get a hematocrit shift  
17 or not. Whether this is in animals, or in clinical  
18 trials with ANP, that is a very hit or miss.  
19 Sometimes you see it, sometimes you don't. It is a  
20 very subtle effect, and it is not quite clear if that  
21 contributes to the hemodynamic actions of BNP or ANP.

22 Anything else?

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1 DR. RODEN: The neurohormonal actions?

2 DR. ABRAHAM: Let's go to backup slide

3 206.

4 DR. RODEN: And what about the mechanism  
5 of the effect of -- on Aldosterone?

6 AUDIENCE: It is known that there are GCA  
7 receptors at the adrenal gland. You can -- in  
8 isolated cell preparations you can inhibit with BNP,  
9 angiotensin II, or ACTH induced aldorelease.

10 DR. ABRAHAM: I think that there is  
11 compelling data in the literature supporting this as  
12 a class effect. There is data for other natrietic  
13 peptides, such as ANP and urodilantin, as well as this  
14 data, and other data.

15 DR. RODEN: We should stop calling them  
16 natrietic peptides.

17 DR. ABRAHAM: These peptide hormones  
18 including BNP. So this data comes from study 325  
19 shown on the top are effects on plasma norepinephrine,  
20 shown on the bottom effects on plasma aldosterone at  
21 baseline, and at six hours for placebo. And the two  
22 main dose groups of -- and the two dose groups of

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1 Natrecor used in the study.

2 And, again, you will see that in regard to  
3 plasma aldosterone, and this is why I was careful to  
4 say that plasma aldosterone is significantly reduced,  
5 because it is, and it is reduced in this as well as  
6 other studies.

7 And I was also careful to say that plasma  
8 norepinephrine is maintained or reduced, because in  
9 these large studies, plasma norepinephrine was not  
10 statistically reduced.

11 In my own protocol 306, which was a single  
12 center study, or perhaps the measurements are done a  
13 little bit more carefully, we did see a significant  
14 reduction in plasma norepinephrine.

15 And in any event, both observations are  
16 consistent with published literature of these peptide  
17 hormones.

18 CHAIRMAN PACKER: Ileana and then Joann.

19 DR. PIÑA: I have a few questions for Dr.  
20 Horton, if she could come back up.

21 DR. LIPICKY: While she is coming up, did  
22 that answer help you, Dan?

1 DR. RODEN: Yes.

2 DR. LIPICKY: Yes?

3 DR. RODEN: I think so. I guess my  
4 decision about whether this compound should be  
5 approved for marketing or not didn't depend on that  
6 answer.

7 But, nevertheless, I wanted to know,  
8 because I think we shouldn't be approving compounds  
9 whose mechanism of action is not thought about, or  
10 completely misunderstood, or not well understood.

11 Because that is sort of asking for trouble  
12 later. And if you have some sense of why it works,  
13 then you might have some sense of what the toxicity  
14 might be later.

15 CHAIRMAN PACKER: Don't go there.

16 (General laughter.)

17 CHAIRMAN PACKER: We could spend three  
18 days on this.

19 DR. RODEN: We will discuss it at lunch if  
20 Milton lets us.

21 DR. PIÑA: Dr. Horton, let me refer you to  
22 your slide number 47, where you have the list of

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1 medications given during Natrecor infusion. And I  
2 heard you use the 60 some percent for ace inhibitors,  
3 but 186 of 505 is not 60 some percent, and I don't  
4 know what this refers to.

5 DR. HORTON: Sure. Let me clarify. This  
6 is actually the numbers of patients who received these  
7 medications during Natrecor therapy in the entire CHF  
8 program, so it is in all eight studies.

9 And, in fact, in most of the earlier  
10 studies, these medications are restricted. If I could  
11 have slide 267, I think this will help.

12 Slide 267, these are the numbers and  
13 percentages of patients who received these medication  
14 before entry into study. So basically those are the  
15 medications that were used within the 24 hours before  
16 receiving study drug.

17 And then the column on the right is  
18 whether those medications were administered during  
19 Natrecor therapy.

20 And first you see that there is a very  
21 high -- well, more than 60 percent of patients, for  
22 example, receiving Dig and ace inhibitors, and it

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1 appears that they continue to be administered those  
2 medications on -- during Natreacor therapy.

3 A similar patterns with non-IV nitrates,  
4 with the antiarrhythmics and with diuretics.

5 DR. PIÑA: That is in one study, that is  
6 in 326?

7 DR. HORTON: Yes, that is the largest  
8 study that studied 305 patients, and it is the one  
9 study which is really the real world study.

10 DR. PIÑA: My other question refers to  
11 your slide number 55 and 56, we are going back to this  
12 management of symptomatic hypotension. You have, on  
13 slide 55, you have 37 patients, and on slide 56, where  
14 you are going through the breakdown of symptomatic  
15 hypotension you have 44?

16 DR. HORTON: Yes.

17 DR. PIÑA: What is the difference in those  
18 two populations, number one. And number two, do you  
19 call intervention for hypotension actually the  
20 administration of oppressor, or is an intervention  
21 simply withdrawal of a Natreacor drug?

22 DR. HORTON: Right. Again I would love to

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1 clarify. In slide 55, this slide represents the  
2 patients that had symptomatic hypotension in the first  
3 24 hours. So -- and then this next slide represents  
4 the numbers of patients who had symptomatic  
5 hypotension at any time during Natreacor therapy, which  
6 may have been up to nine days, or within five hours  
7 after it was discontinued.

8 So there are more events, there are 44  
9 events, as opposed to the 37 events which were  
10 observed in the first 24 hours.

11 So, number one, that tells you that most  
12 symptomatic hypotension is identified within the first  
13 24 hours. But this slide really is more comprehensive  
14 and allows for us to really say what happens to all  
15 patients who develop symptomatic hypotension during  
16 this time frame.

17 Now, the previous slide only talks about  
18 the greatest effect on Natreacor dosing, whether there  
19 was no change, whether it was decreased, or whether it  
20 was discontinued.

21 This slide, in contrast, when I talked  
22 about intervention, I -- the definition of

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1 intervention is the administration of an inotrope or  
2 oppressor in response to the symptomatic hypotension.

3 Patients who had Natreacor decreased or  
4 discontinued are not represented here. They are  
5 represented on the slide, but they are represented as  
6 no intervention.

7 DR. PIÑA: So, in other words, if I  
8 understand this correctly, the 37 patients had their  
9 blood pressure abnormality within the 24 hours, that  
10 means there are seven patients that became hypotensive  
11 after?

12 DR. HORTON: After 24 hours.

13 DR. PIÑA: And off drug?

14 DR. HORTON: No, it would have been after  
15 24 hours, and within five hours after Natreacor was  
16 discontinued. So it might have happened in patients  
17 who got drug for three days, sometime after 24 hours.

18 I included the symptomatic hypotension  
19 that occurs within five hours because I wanted to be  
20 fair, and to be -- take a conservative approach, that  
21 is to implicate that hypotension that might happen  
22 within five hours after Natreacor is discontinued could

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1 still be potentially related to Natreacor therapy.

2 DR. PIÑA: Thank you. And I have a  
3 question for Bill.

4 Bill, you've been talking about the real  
5 world. In the real world most patients are not  
6 adequately treated, even with good old ace inhibitors,  
7 much less anything else.

8 And one of the reasons that we would use  
9 a short term compound, other than to obviously make  
10 the patient feel better, and you have them in the  
11 hospital for a reason, because they are ill, is to  
12 have the opportunity to up-titrate other drugs that  
13 you will eventually hopefully put them on, and send  
14 them home.

15 Where do you see the drug of this agent  
16 for that real world use?

17 DR. ABRAHAM: Yes. I think that this  
18 agent can also be viewed as a bridging agent. And, in  
19 fact, we need to think of all IV agents for the acute  
20 management of heart failure as bridging agents.  
21 Because as we have demonstrated, in lots of clinical  
22 pharmacology studies, if you don't do anything else

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1 when you turn the drip off, the patient goes back to  
2 their decompensated baseline.

3 I believe the experience in ace inhibitor  
4 treated, and other vasodilator treated patients is  
5 substantial, and that as is typical of our practice,  
6 we start low and we go slow, and take an incremental  
7 approach to try to wean patients off of their  
8 dependence of the intravenous agent, and on to an  
9 adequate oral medical regimen.

10 That is not to say where there may not be  
11 some instances, particularly in the low blood pressure  
12 patients, where we might have to resort to an inotrope  
13 as a way to bridge them to that oral therapy.

14 I don't think all patients will be  
15 successfully treated with, or bridged to oral therapy  
16 by a vasodilator in general, or Natreacor in  
17 particular.

18 CHAIRMAN PACKER: You had a specific  
19 follow-up on that, or this is for later?

20 DR. PIÑA: Specially since I'm not bowled  
21 over by diuresis here, either. And, obviously, there  
22 was more conservative views of diuretics while the

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1 drug was going on, but it is certainly not addressing  
2 the volume stats.

3 CHAIRMAN PACKER: Ileana, you had another  
4 follow-up? We will go to Joann and then to Jay.

5 DR. LINDENFELD: Clarification. In your  
6 real world study 326, despite the use of Dobutamine  
7 there was no difference in heart rate, is that  
8 correct?

9 DR. HORTON: I am sorry, say that again?

10 DR. LINDENFELD: There was no difference  
11 in heart rate at six hours, or 24 hours?

12 DR. HORTON: Despite the use of  
13 Dobutamine, did you say?

14 DR. LINDENFELD: In the real world group,  
15 in the control group.

16 DR. HORTON: I'm sorry, I'm not  
17 understanding your question. Are you asking me if --

18 DR. LINDENFELD: Well, Bill made the  
19 comment that there may be a decreased rate pressure  
20 product with this drug, and certainly pressure is  
21 less. But it didn't appear to me that there was any  
22 difference in standard care versus Nesiritide and

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1 heart rate.

2 DR. HORTON: The information that was  
3 shown comparing the effect on heart rate was from a  
4 placebo controlled study, not a Dobutamine control  
5 study.

6 DR. LINDENFELD: I think on page 76,  
7 standard care versus Nesiritide at 3 hours, there is  
8 no difference in heart rate versus your standard care  
9 in this drug. So I don't think we can say much about  
10 heart rate being of benefit here. Page 76 in the FDA  
11 book, bottom of the page.

12 Blood pressure is less, certainly, but we  
13 can't say too much about heart rate, I don't think you  
14 are comparing to a real world look.

15 DR. HORTON: That is correct that there is  
16 no change compared to IV vasoactive therapy overall,  
17 but a little more than half received Dobutamine,  
18 correct.

19 DR. LIPICKY: So when we pick out  
20 patients, I'm not sure we can use that.

21 Just help me with, in study 325 we are  
22 still interested in creatinine. In study 325, within

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1 the first six hours, 14 and 17 percent of the two  
2 Nesiritide doses required some specific intervention  
3 for renal insufficiency? That is what it says on page  
4 65, zero percent in the placebo group, 6 patients are  
5 14 percent in the low dose, and 7 are 17 percent in  
6 the high dose that required some specific intervention  
7 short of dialysis.

8 That is a little bit of a concerning  
9 number in just six hours.

10 CHAIRMAN PACKER: Can you repeat those  
11 numbers again, Joann?

12 DR. LINDENFELD: Yes, it is in study 325,  
13 this is on page 65, medical intervention without  
14 dialysis, such as IV fluid boluses and medication  
15 changes were required in 0 of 42 placebo patients, 6  
16 of 43 or 14 percent of the low dose, and 7 or 17  
17 percent of the higher dose.

18 CHAIRMAN PACKER: Is this the one that has  
19 the nominal P values, .033?

20 DR. LINDENFELD: It just says requirement  
21 for intervention due to worsening renal failure. That  
22 is throughout. I wonder why it was higher here, and

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1 then --

2 DR. GROSSBAR: I'm just trying to correct  
3 an earlier comment. My friend Dr. Massey informs me  
4 that on the Dobutamine question earlier that there was  
5 an increase in heart rate in the Dobutamine group by  
6 several beats per minute. The P value was .05  
7 something, so it may not be an overwhelming proof of  
8 that effect, it is not proof of no effect.

9 DR. LIPICKY: So I just want to get back  
10 to this point about in 325 why we saw all this need  
11 for intervention for renal failure, and we didn't  
12 subsequently?

13 This is a fair number of patients that  
14 required specific intervention.

15 DR. ALLGREN: I believe you are talking  
16 about the table in study 325 of people giving  
17 interventions for the rising creatinines, such as  
18 fluid boluses or maybe making a change in the  
19 medication.

20 I think that is reflecting the issue that  
21 Dr. Horton had talked about with regard to the rising  
22 creatinines. I believe if we look at that same

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1 intervention, we are trying to pull it up for study  
2 326, it was fairly balanced across the groups in that  
3 study.

4 DR. LINDENFELD: And then just --

5 CHAIRMAN PACKER: Before we leave that,  
6 just so we can clarify, 326 was active control, so if  
7 the active control had an adverse effect on  
8 creatinine, one would not pick that up. So 325 is  
9 placebo control, the data I think that Joan --

10 DR. ALLGREN: Really only for the first  
11 six hours in that study.

12 CHAIRMAN PACKER: Right. I guess that the  
13 data -- this is from Dr. Throckmorton's review. Also  
14 it is a two percent incidence of interventional  
15 placebo, 14 percent on low dose, and 21 percent,  
16 actually, on high dose.

17 DR. ALLGREN: I just want to be sure it is  
18 clarified that those are interventions throughout day  
19 21 in the study, it is not talking about just the  
20 first six hours.

21 CHAIRMAN PACKER: I see.

22 DR. ALLGREN: In both studies 325 and 326.

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1 DR. GROSSBAR: And except for the first  
2 six hours, in 325, all those patients were crossed  
3 over to typical standard therapies. So it is -- it is  
4 not a six hour event, and it is cumulative, and it is  
5 not against the placebo, it is generally against the  
6 population.

7 DR. LINDENFELD: Just to clarify, how  
8 often was creatinine measured in 325 compared to 326,  
9 were they the same?

10 DR. HORTON: They were the same, they were  
11 measured daily through the duration of pre-renal  
12 vasoactive therapy.

13 DR. LINDENFELD: And then a question about  
14 sodium. This comes up to how effective is this drug,  
15 in some patients creatinine is increased, and I was  
16 concerned to learn that along with that there is a  
17 trend, a pretty good trend for sodium to be decreased,  
18 particularly in the long term study.

19 It bothers me a little bit in a drug where  
20 we think that although we are not going to claim that  
21 it has naturietic actions, that there is this sort of  
22 suggestion that this is great for the kidneys.

1           On page 151 of the briefing document,  
2           there is a trend at least towards a dose dependant  
3           decrease in mean serum sodium, and in the Nesiritide  
4           groups.

5           DR. HORTON:    Could I have backup slide  
6           346, please?  This slide looks at the overall changes  
7           from baseline at the time of the last available lab  
8           value.  And my conclusion, from this slide would be  
9           that there is no clinically significant difference,  
10          and the difference is not different in the treatment  
11          groups.

12          DR. LINDENFELD:  We've got different  
13          numbers, I think, do we, or are they -- the table I'm  
14          looking at is in the bottom of 151, where we show for  
15          control minus .4 sodium, minus .8, minus 1.2, and  
16          minus 1.8 over the three doses of Nesiritide.

17                 One is actually day two and one is last  
18                 available, also.  So through day two there appears to  
19                 be at least a fairly substantial trend with dose --

20          DR. ABRAHAM:  I guess I might view this  
21          data similarly to how we are looking at the naturietic  
22          effect of this agent.  In fact, in some ways, it

1 suggests that there may be a modes naturietic effect,  
2 because this is what we see routinely when patients  
3 are given standard naturietic or saluretic agents, and  
4 replace some of their volume loss with free water.

5 But I don't want to make that leap of  
6 faith and come to that conclusion except to say that  
7 in some ways, you know, perhaps this data is not fully  
8 reliable, or we are making more out of it than we  
9 should, given such a heterogenous response. It  
10 depends on when you look, it depends on which study  
11 you look at, whether or not you even see this effect  
12 on sodium.

13 DR. HORTON: Actually, if I could have  
14 backup slide 305, please?

15 Given the different time points, the  
16 different populations that we are looking at, this is  
17 a measure of the clinically significant adverse events  
18 that the investigator reported. The fourth line there  
19 is hyponatremia, so these are adverse events related  
20 to laboratory values.

21 And you can see that there is no  
22 difference, no clinically -- no difference in the

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1 groups, but in fact there is less hyponatremia  
2 reported. Our conclusion would be that there is an  
3 insignificant effect, that there is no effect.

4 DR. LIPICKY: There is no creatinine up  
5 here?

6 DR. HORTON: I already gave you that  
7 information, that is in 6 and 10 percent of patients  
8 in the Natrecor groups.

9 DR. LIPICKY: Those point estimates are  
10 smaller than whatever it is, standard deviation, or  
11 standard error that is next to it. If I looked at  
12 that table I would have said there was nothing there.

13 Why do you really think there is something  
14 there?

15 DR. LINDENFELD: Well, there is a comment  
16 here that there is a trend towards --

17 DR. LIPICKY: Well, ignore the comment,  
18 look at the numbers.

19 DR. RODEN: I hate to agree with Ray, but  
20 if the serum sodium in a patient with heart failure  
21 goes from 132 to 131, I don't think that is clinically  
22 significant. I don't think that tells you that it is

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1 a naturietic peptide, either.

2 DR. LIPICKY: But this is not a clinically  
3 significant argument. I think these are just numbers.

4 DR. PIÑA: And I don't think you can make  
5 any statements about iso or hypotonic volume, because  
6 the volume didn't change much in any of these  
7 patients, including the intake, which was pretty  
8 constant throughout the whole time.

9 CHAIRMAN PACKER: Jay?

10 DR. ABRAHAM: I apologize for speculating  
11 on the mechanism of that.

12 CHAIRMAN PACKER: Jay?

13 DR. COHN: I would like to get back to the  
14 concomitant therapy issue, because in the real world,  
15 so called real world study that you've shown us, ace  
16 inhibitors were given to only 62 percent of the  
17 patients prior to intervention with Natrecor.

18 Diuretics were being used in about 82  
19 percent, I think, which strikes me as somewhat  
20 surprising that it isn't 100 percent, since these  
21 people are obviously all in severe enough heart  
22 failure to require hospitalization, and yet 18 percent

1 of them weren't getting diuretics, and 38 percent  
2 weren't getting ace inhibitors.

3 It gives you a unique opportunity, though,  
4 despite the fact that I'm trouble by what was pre-  
5 existing therapy, to look at the relationship between  
6 Natrecor side effects, and adverse events, and co-  
7 therapy. That is, is there any evidence that those  
8 patients on an ace inhibitor had a greater incidence  
9 of hypotension, and in fact we would like to think  
10 that 100 percent of patients who get subjected to this  
11 therapy are going to be on an ace inhibitor, and the  
12 incidence of that, therefore, might be higher.

13 Also the incidence of use of beta blockers  
14 was, of course, very low in this study. And yet that  
15 may become a much more common phenomenon in the future  
16 that these patients are going to come in being on a  
17 beta blocker.

18 So I would like to hear something about  
19 interaction, if you will, with co-existent therapy for  
20 heart failure, especially in significant doses, and  
21 maybe some explanation of why only 62 percent of these  
22 people, in what I assume were pretty formidable

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1 centers, it may not be the real world, but it is  
2 probably the real world in the centers in which you've  
3 done this trial.

4 Why so few of the patients were on what we  
5 would consider to be optimal therapy for heart  
6 failure?

7 DR. HORTON: Yes. I think I can clarify  
8 that point. To understand the limitations of how that  
9 data was collected, medications prior to study, and  
10 the slide I showed you, the 62 percent and 82 percent,  
11 those are actually medications that were administered  
12 within 24 hours before entry into the study.

13 So it was not a question of what is the  
14 patient's chronic cardiovascular regimen. And, in  
15 fact, patients who were non-compliant with the regimen  
16 would not show up in that table, because if they did  
17 not receive the medication, or if there was not  
18 evidence that the patient received that medication, in  
19 the medical record, it is not reflected on that slide.

20 DR. COHN: So you really don't know what  
21 the therapy was in the stable period of time before  
22 the patient entered into the trial?

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1 DR. HORTON: I know that they had to have  
2 received at least 62 -- at least 62 percent of  
3 patients had to have been receiving an ace inhibitor,  
4 and at least 82 percent of patients had to have  
5 received a diuretic during the 24 hours.

6 DR. COHN: But it may have been much  
7 higher than that, obviously?

8 DR. HORTON: Yes.

9 DR. COHN: If an ace inhibitor, long  
10 acting ace inhibitor had been used 25 hours before  
11 your study, I assume it wouldn't show up, and yet this  
12 patient is still potentially having an effect from the  
13 ace inhibitors, is that right?

14 DR. HORTON: That's correct.

15 DR. GROSSBAR: Darlene can speak to the  
16 interaction question, and I don't want that to get  
17 lost. But it would probably be even problematic to  
18 characterize a patient who is on Lasix but not taking  
19 it.

20 Unless heart failure has changed in the 15  
21 years since I was a house officer, that was a very  
22 common reason why people ended up in the hospital,

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1 they simply stopped taking the medicines they were on.

2 So I don't know if it is a commentary on  
3 the center, or on the population of patients who show  
4 up at a center. And all we wanted to know was what  
5 their status was beforehand, I don't know what we  
6 would do with information that said that they were on  
7 Laxis but not taking it.

8 DR. COHN: But it would be very hard to  
9 get into an emergency room with worsening heart  
10 failure and not get a dose furosemide in the emergency  
11 room.

12 So the fact that they weren't getting a  
13 diuretic prior to entry into this protocol is still  
14 somewhat surprising, even if they were non-compliant  
15 outside.

16 DR. GROSSBAR: But we do have interaction  
17 information which we --

18 DR. HORTON: Could I have slide 300,  
19 please? This slide shows the four adverse events that  
20 are consistently reported more frequently with  
21 Natrecor, and their association in patients who either  
22 were receiving an ace inhibitor, or not receiving an

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1 ace inhibitor.

2 And what you see here is that there may be  
3 an increase in symptomatic hypotension with  
4 concomitant administration of an ace inhibitor. And  
5 that is consistent with the fact that both are  
6 vasodilators, and that they should be used with  
7 caution, and that certainly blood pressure should be  
8 monitored, specially when the peak effects of the  
9 concomitant medication are expected.

10 But you also see that they are generally  
11 well tolerated with 90 percent of patients who are  
12 receiving an ace inhibitor, not experiencing  
13 symptomatic hypotension.

14 CHAIRMAN PACKER: Any other questions,  
15 Jay? I guess not. Does anyone else have any  
16 questions for either of the two presentations? Cindy?

17 DR. GRINES: I just have a real quick  
18 question about the creatinine elevations. And you had  
19 shown a slide demonstrating that they weren't more  
20 frequent in patients with a systolic blood pressure of  
21 less than 85, but for heart failure patient that might  
22 be pretty normal.

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1                   And I wondered if you had any information  
2 with regard to patients with profound hypotension,  
3 perhaps those less than 70, or patients who had  
4 sustained hypotension for more than a couple of hours?

5                   DR. HORTON: I'm sorry, we didn't look at  
6 it in that way.

7                   CHAIRMAN PACKER: Let me ask, and is to  
8 either of the two speakers. The proposed labeling for  
9 this drug actually suggests that the word rapid be  
10 included in the description of the effect of the drug  
11 on both hemodynamics and symptoms.

12                   In a conventional intensive care unit  
13 setting, physicians are used to thinking of rapid as  
14 minutes. And all the drugs that Bill mentioned are  
15 agents that work very, very quickly, either because  
16 they intrinsically work very quickly, or because they  
17 are given as a bolus followed by an infusion.

18                   So that almost all the agents that we used  
19 in an intensive care unit work within five minutes,  
20 ten minutes. And peak about that same time.

21                   This is an agent that works, or appears to  
22 work more slowly, and that peaks at three hours, and

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1 that people shouldn't increase the dose of this drug  
2 in an interval less than three hours.

3 Do you think the word rapid is  
4 appropriate?

5 DR. HORTON: Yes. Your reference to other  
6 agents that work within minutes to a half hour or so,  
7 must obviously be in relation to its hemodynamic  
8 effect. And, in fact, the onset of action of Natrecor  
9 is within about 30 minutes, so you can see decreases  
10 in wedge earlier than that. But statistically  
11 significant are seen in 30 minutes in the early  
12 studies.

13 When we got to the pivotal studies the  
14 first measurement of central hemodynamics was either  
15 one hour, one and a half hours in the two pivotal  
16 studies.

17 At both of those time points the effects  
18 on wedge are statistically significant, and that was  
19 the first time point that was measured.

20 With regard to symptoms, the first I mean  
21 point that we mentioned symptoms was at six hours.

22 CHAIRMAN PACKER: I don't disagree with

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1 when you collected the data, I'm just wondering  
2 whether in the conventional sense physicians will  
3 think that rapid means something other than what the  
4 data base would support.

5 DR. HORTON: I think Bill should answer  
6 that one.

7 DR. LIPICKY: I think that word will  
8 disappear, Milton.

9 CHAIRMAN PACKER: Okay. You don't have to  
10 answer it, Bill.

11 DR. ABRAHAM: Okay.

12 CHAIRMAN PACKER: And one related question  
13 to the proposed wording for labeling, the sponsor is  
14 proposing initiation of therapy at an infusion rate of  
15 0.015, and I believe that the wording being proposed  
16 by the sponsor is if a further hemodynamic effect is  
17 desired, that the dose would be then increased to  
18 0.03. Is that correct?

19 DR. HORTON: Up to point zero --

20 CHAIRMAN PACKER: Right, or up to. How  
21 would one know how to do that if you didn't measure  
22 hemodynamics, which is what you are saying physicians

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1 need not do?

2 DR. HORTON: Right. Within the context of  
3 routine heart failure clinical management, the way  
4 that these, as you know, I'm embarrassed to be saying  
5 this to you, that the way these patients are managed  
6 is that your goal is to achieve symptom improvement  
7 and rapid hemodynamic improvement.

8 There are patients that you don't have  
9 central hemodynamics for which you are fairly certain,  
10 by a number of clinical measures, peripheral  
11 circulation, dyspnea, capillary refill, jugular venus  
12 distension, that you know that you haven't achieved  
13 the hemodynamic results that you aimed to do.

14 And so you may titrate the agents that you  
15 now have currently available to you.

16 CHAIRMAN PACKER: It can't be symptoms,  
17 because you haven't shown a dose response on symptoms.

18 DR. HORTON: Right. You are absolutely  
19 right. It is clear that there is no dose response in  
20 symptoms, although both doses do cause significant  
21 symptom improvement by six hours.

22 This is really a question that is left up

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1 to individual physicians. And if for some reason they  
2 want to achieve a better hemodynamic endpoint, and the  
3 drug has been tolerated at .015, that those patients,  
4 that physician should be allowed to increase the dose  
5 to achieve that.

6 CHAIRMAN PACKER: I have no problem with  
7 allowing physicians the -- to use their judgement in  
8 this regard, which I think inevitably they would do.  
9 It is just that there seems to be some inconsistency  
10 in thinking through the process of what would lead a  
11 physician to do that if, as you indicate, or as you  
12 suggest, they need not use invasive hemodynamic  
13 measurement, the clinical responses are not dose  
14 dependent.

15 How would someone not using the Swan-Ganz  
16 catheter ever make the decision to increase the dose?

17 DR. GROSSBAR: I believe that our position  
18 in making that recommendation was simply to reflect  
19 the information that we had provided, and that  
20 recognizing that there are many patients who are  
21 monitored with PA catheters, and whose wedge pressure  
22 is followed and managed with current agents, whether

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1 it is nitroglycerin, or nitroprusside, or what not, we  
2 wanted to at least allow the opportunity for those  
3 patients to be aware that there was a possible  
4 increased hemodynamic benefit, and to characterize the  
5 potential increased hemodynamic risk, and not to  
6 exclude that possibility by virtue of labeling, and  
7 have it left to a situation where people say, none of  
8 you people pay attention to the label, anyway, we  
9 shouldn't worry about it.

10 So we are simply characterizing it, if you  
11 manage patients this way, this is the way to manage  
12 them.

13 DR. LIPICKY: I guess just an information  
14 thing. Is there some relationship between the jugular  
15 venus pressure and the pulmonary capillary wedge  
16 pressure?

17 CHAIRMAN PACKER: I will just take a shot  
18 at this. I think the answer is, in general there may  
19 be. It is not consistent because, in fact, the  
20 dynamics on the right and left side may be different,  
21 and that may be particularly true in acute ischemic  
22 states.

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1           So I think the answer to that is, you  
2 know, sometimes there is, but I'm also struck by the  
3 fact, if I remember, right atrial pressure, which is  
4 what jugular venus pressure is reflecting, was  
5 measured in the trials, but the effect on pulmonary  
6 wedge pressure at 24 hours was more striking, and more  
7 consistent.

8           DR. COHN: I think the answer to that  
9 question is that in chronic heart failure, that the  
10 two do track together. In acute ischemic events they  
11 clearly do not.

12           CHAIRMAN PACKER: For those who aren't  
13 involved in the area of heart failure, the discussion  
14 which is occurring now is a familiar one to many of  
15 us.

16           DR. STEVENSON: We looked at 1,000  
17 patients, and the correlation at baseline between  
18 atrial compression wedge is .67, the correlation of  
19 the changes in the two was .65, so it is not exact, it  
20 does track together.

21           DR. ABRAHAM: I guess I'll just add, and  
22 all of you know this better than I do, it is really

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1 the whole package that you are looking at here, and we  
2 call that clinical judgement. It is not just the neck  
3 veins, it is not just the blood pressure, it is not  
4 just the symptoms, but it is the whole package.

5 And I think titratability of any drug just  
6 acknowledges the fact that when we look at averages in  
7 clinical trials, we also need to acknowledge that  
8 individual patients respond individually to any drug,  
9 or any given dose of a drug.

10 CHAIRMAN PACKER: Dan?

11 DR. RODEN: This is a question that will  
12 come up in the questions, and traditionally we don't  
13 ask your advice during the questions, so I would like  
14 your advice to me now.

15 Defend the lack of a bolus, and defend the  
16 fact that the starting dose is a dose that looks like  
17 it is at the top of the dose response curve for at  
18 least some measures in some studies. And shouldn't  
19 the starting dose, therefore, be lower?

20 DR. ABRAHAM: Yes. There are two studies  
21 that I fall back on. And, again, this is from the  
22 clinician and clinician investigator standpoint.

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1           And those are the early phase II studies,  
2           306 and 307, looking at infusion without a bolus, and  
3           looking at incremental doses across a dose range,  
4           starting with a low dose below the current recommended  
5           doses.

6           And I think you do see a dose response in  
7           that study, which sort of defines the low to the high  
8           end of the dose response curve.

9           And, again, in our own work, from protocol  
10          306, the onset of action to significant reduction in  
11          wedge pressure is seen within 15 to 30 minutes  
12          without a bolus.

13          And so my impression is, and this is not  
14          data driven, these are small studies with small  
15          numbers of patients totaling 36 altogether, is that  
16          the bolus dose is not necessary, and we have defined  
17          a reasonable dose range.

18          CHAIRMAN PACKER: We will hold here. I'm  
19          afraid that my watch stopped a while ago. So I didn't  
20          realize what time it was. We will take 20 minutes,  
21          hopefully no further lunch break and reconvene at that  
22          time.

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(Whereupon, at 1:30 p.m. the above-entitled matter was recessed for lunch.)

1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (2:00 p.m.)

3 CHAIRMAN PACKER: No introduction, but  
4 simply go forward to question number 1.

5 Trials 311, 325, 326 received the greatest  
6 attention from the sponsor and the reviewers, and  
7 received the greatest attention at today's meeting.  
8 Were the results of the five other trials, these were  
9 smaller, pilot trials, sufficiently consistent with  
10 the results of these three that today's discussion can  
11 be limited to 311, 325 and 326, or are there  
12 disparities that need to be reconciled?

13 We will call on our primary reviewer to  
14 summarize his thoughts and see if the Committee agrees  
15 or disagrees.

16 DR. KONSTAM: I don't see any disparities  
17 with the other studies that raise attention.

18 CHAIRMAN PACKER: Does anyone disagree?

19 (No response.)

20 CHAIRMAN PACKER: Question number 2, how  
21 should the patient population of trials 311, 325, 326  
22 be characterized? Was it a typical population of

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1 patients with chronic congestive heart failure,  
2 sufficiently decompensated (from any cause) to require  
3 hospital admission for the treatment of that  
4 decompensated?

5 Marv?

6 DR. KONSTAM: Yes, I think that is a  
7 little difficult, and we have been through discussions  
8 about this. I think it is clearly a population of  
9 patients, both 311 and 325 clearly are populations who  
10 have -- who are sick with heart failure. I think 325  
11 all we really have to go on in this is the fact that  
12 entrance criteria required this phrase of  
13 decompensated sufficiently to require intravenous  
14 therapy.

15 I, you know, it is not precisely the  
16 population that we most might want to use the drug in,  
17 but I'm not sure, honestly in my own mind, that we can  
18 do any better than that.

19 So I don't know how to characterize it any  
20 better than that.

21 DR. RODEN: Marv, are you referring to  
22 acute MI patients when you say that, or just --

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1 DR. KONSTAM: I'm sorry, I don't --

2 DR. RODEN: When you are talking about  
3 from any cause.

4 DR. KONSTAM: No.

5 DR. RODEN: Are you including acute MI  
6 patients?

7 DR. KONSTAM: No, I'm sorry. I mean,  
8 certainly not. You wouldn't -- no, there is no  
9 representation of patients with acute MI, I'm sorry.

10 CHAIRMAN PACKER: In that regard I think  
11 we can all conceive of studies that can be done in  
12 patients with acute MI that would shed light on  
13 efficacy and/or safety. There are no data on patients  
14 with an acute MI in this data base.

15 We have discussed that deficiency earlier.  
16 How much of a deficiency do you think that is, and how  
17 should the absence of that affect either approval or  
18 labeling?

19 DR. KONSTAM: Yes. Again, just give my  
20 opinion about it. I'm not that troubled by it. I  
21 feel as though the sponsor made a decision to  
22 constrain the population in that way. It is a common

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1 judgment.

2 I agree that there is concern, you know,  
3 with the implication, that there is concern that once  
4 approved the drug might be used in acute MI, but I  
5 think that we could -- the sponsor, you know, in the  
6 labeling, would clearly state there is no experience  
7 justification or knowledge about the adverse effects  
8 that might result.

9 And I think that my own opinion about it  
10 is that to the extent that we are concerned as a  
11 committee I think it would probably impact more on  
12 what we would like the sponsor to do after approval,  
13 than approvability per se.

14 CHAIRMAN PACKER: And before we just open  
15 it for discussion, so that we can just complete the  
16 line of reasoning, to what degree is your sense of, I  
17 shouldn't say comfort with the absence of acute MI  
18 data, but willingness to see that pursued post, as  
19 opposed to pre marketing related to the fact that it  
20 is a vasodilator would you feel differently if it had  
21 a different mechanism of action?

22 DR. KONSTAM: No, I wouldn't feel

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1 differently.

2 CHAIRMAN PACKER: General discussion on  
3 this. Jay?

4 DR. COHN: I think that the absence of  
5 data in an ischemic population is of some concern  
6 because many patients who present this way may have  
7 subclinical ischemia that is unrecognized, and it  
8 would be reassuring to know that there was no adverse  
9 events taking place in patients who are having  
10 unstable angina, or acute MI, or having even silent  
11 ischemia.

12 I think we can probably assume, from  
13 previous experience, that that is not going to be the  
14 case, but it is a deficiency in the package, and would  
15 obviously require that that group not be treated.

16 DR. KONSTAM: Just another comment about  
17 the patient population. It strikes me that patients  
18 who are hospitalized for worsening failure, who are  
19 congested, which is the prerequisite for entry into  
20 these protocols, are patients who are to be considered  
21 for therapy, aggressive treatment, are always patients  
22 who have failed diuretics. At least inadequate

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1 response to aggressive attempts at diuresis.

2 And I think the population that was  
3 entered into this protocol, by design, and I  
4 understand the reason for it, this is an incredibly  
5 difficult patient population in whom to do a control  
6 trial.

7 But by design these were patients who had  
8 not been necessarily aggressively treated with  
9 diuretics and had failed, and in fact, it was a  
10 prerequisite in the protocol to stop the therapy some  
11 hours before the trial was undertaken.

12 So it seems to me that this is really not  
13 the population that those of us around the table would  
14 choose to use a drug other than a diuretic until the  
15 patient had failed to respond adequately to the  
16 diuretic.

17 And I think that is a deficiency, it may  
18 be an unavoidable deficiency, but it raises real  
19 concerns about the population who you are going to  
20 eventually utilize the drug in.

21 CHAIRMAN PACKER: Is there any more  
22 discussion on patient population? I must say I, for

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1 one Marv, I guess I'm more distressed than you are  
2 about the absence of data in patients with acute  
3 myocardial infarction.

4 I think that the risk to benefit  
5 relationship may be different in the acute ischemic  
6 setting. Now, having said that, it is a little bit  
7 hard to calculate that in any reasonably sized trial,  
8 because the benefit here may or may not be based on  
9 hemodynamic, and therefore harder to quantify relative  
10 to any identifiable risk, and how large is the study  
11 in acute ischemic settings have to be to identify  
12 quantifiable risk.

13 I would say that, and this perhaps reveals  
14 an inappropriate bias, and that is that I guess I'm a  
15 little bit more reassured by the fact that it is a  
16 vasodilator. I might not be so reassured if it  
17 weren't. And I think that is -- I think that that is  
18 a bias which is revealed from the Committee's  
19 deliberations from a year ago, when we recommended  
20 that certain relabeling be pursued for IV positive  
21 inotropic drugs, but not for IV vasodilators.

22 So I think that we may, in fact, be guided

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1 by what we think is the mechanism of action here, but  
2 I for one would not like to send this signal to the  
3 community that the absence of acute MI data here is  
4 acceptable, because I feel that a substantial  
5 percentage of patients who come in with acute heart  
6 failure have an acute ischemic settings, they are not  
7 enrolled in these trials, because they are excluded  
8 from these trials.

9 DR. KONSTAM: Let me just respond to that.  
10 I mean, I agree completely that we don't have any  
11 safety or comfort measure around the use of this agent  
12 in acute MI.

13 I agree with that wholeheartedly, and that  
14 is a considerable issue. I guess, you know, where  
15 maybe we differ a little bit, is just our personal  
16 response to that in terms of what a sponsor needs to  
17 do in developing a drug for acute decompensation of  
18 heart failure.

19 My own bias about it is that if I were  
20 very, very confident about the safety and efficacy of  
21 a drug for management of acute heart failure, in a  
22 program that had excluded acute MIs, I would say I

1 know nothing about this in acute MIs, now go do a  
2 post-marketing study.

3 But I think that that is really a very  
4 subjective decision.

5 DR. PIÑA: I think your point is well  
6 taken, Milton, and it is underscored by the fact that  
7 we know that drugs that are not necessarily approved  
8 for one thing will be used for that use, regardless of  
9 what we say here.

10 CHAIRMAN PACKER: I mean one of the things  
11 is we can recommend to Ray and the division that  
12 specific wording be put in that there is no data in  
13 patients with acute myocardial infarction, and  
14 undoubtedly that should be done, and undoubtedly that  
15 will be done, and undoubtedly it won't make any  
16 difference, whatsoever.

17 Yes, we will -- Ray, we want you to do  
18 this, we want you to make it perfectly clear we have  
19 no idea whether what we have just requested you to do,  
20 or recommended that you do will be meaningful in  
21 clinical practice.

22 DR. LIPICKY: I understand that, and we

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1 will do as you direct. And do you care about  
2 systolic/dystolic dysfunction?

3 CHAIRMAN PACKER: Is that a global  
4 philosophical question, or with respect to --

5 DR. LIPICKY: No, you don't have to answer  
6 that.

7 CHAIRMAN PACKER: Okay. Cindy?

8 DR. GRINES: I guess I would also like  
9 some additional data in the ischemic heart disease  
10 population, but I'm not quite as concerned, because I  
11 think we've all been, you know, sort of inundated with  
12 ace inhibitors for acute MI, and you know, nitro,  
13 etcetera.

14 I can't imagine that anybody is going to  
15 choose a drug like this for a first line agent for  
16 acute Mi.

17 And then the second thing is that, well,  
18 maybe they will, but there are so many other proven  
19 therapies that reduce mortality.

20 The other thing is that I think when you  
21 get a complicated acute MI patient he is very unlikely  
22 to stay in a very small community hospital without a

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1 Swan.

2 We get a lot of those patients  
3 transferred. So I think it is less likely that a  
4 family practitioner, somebody who is less experienced  
5 will be caring for them.

6 CHAIRMAN PACKER: Number 3, in patients  
7 who, like those studied, what is the dose response  
8 relationship, if any, between Nesiritide and decreases  
9 in pulmonary capillary wedge pressure. And then go on  
10 to answer all three subquestions; how long does this  
11 effect last, how does the effect compare to that of  
12 convectional therapy, and what are the data to support  
13 your conclusions.

14 DR. KONSTAM: Yes, I think this is a  
15 source of some discomfort, because we don't have clear  
16 indication from the pivotal trials precisely what is  
17 the dose response with regard to wedge pressure of  
18 this agent, particularly within 311, there doesn't  
19 seem to be any benefit of the .03 dose compared to the  
20 .015 dose. In fact, some of the data looked like it  
21 goes in the other direction.

22 And so some of the other trials look like

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1 there is a dose response around that dosing, but it  
2 is not quite clear. So I'm left not quite sure of  
3 that.

4 As far as how long does this effect last  
5 during continuous administration, we do see up to 24  
6 hours in protocol 311, the wedge pressure effect is  
7 there, clearly, although I think that there is some  
8 loss of effect at 24 hours, as Dan has pointed out, it  
9 is not clear whether that is a pharmacokinetic issue,  
10 or pharmacodynamic issue.

11 How does this affect compared to  
12 conventional therapy? I don't think we have any idea  
13 about that, because we don't have any comparative  
14 hemodynamic data with conventional therapy.

15 And that is it.

16 CHAIRMAN PACKER: Three actually does need  
17 to be ever addressed, you already citing the data for  
18 the first three questions.

19 Discussion on the effects of the drug on  
20 pulmonary wedge pressure, is there agreement or  
21 disagreement with Marv's conclusions?

22 DR. COHN: Let me make a few comments

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1 here. In lieu of my consultants, bypass, let me make  
2 a few comments, because I think they are pertinent  
3 here.

4 I'm very sympathetic to this drug for a  
5 lot of reasons. And they really go back many years  
6 with my -- some of the early studies that we did with  
7 atrial peptide.

8 The virtue of this drug was, at that time,  
9 or this group of agents, this peptides, was at that  
10 time that they were vasodilator, they were naturietic,  
11 and they were neurohormonal inhibiting.

12 And that is a very attractive profile.  
13 Unfortunately despite my sympathy for the concept, the  
14 data really have not borne out the original  
15 hypothesis, that these drugs would indeed have  
16 significant naturietic and diuretic effect in this  
17 patient population, that they would significantly  
18 inhibit neurohormonal mechanisms which are pretty  
19 borderline at best; and that they were potent  
20 vasodilators that would be predictable and titratable.

21 So the weaknesses in the data, I think,  
22 reflect the fact that the initial enthusiasm for the

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1 multiple effects of this, physiologic effects of this  
2 class of drugs has not been borne out in the patient  
3 population that we are using it in.

4 Now, one of the fascinating things about  
5 this drug, it is an endogenous peptide. Now, that is  
6 wonderful from the standpoint of safety, but it places  
7 potentially a burden on the sponsor, because you are  
8 not studying the dose response of a foreign agent, you  
9 are studying adding BNP to already existing BNP  
10 levels.

11 And, therefore, the dose response is  
12 really the response as you increased the dose of --  
13 the circulating levels of BNP, and in fact, we have no  
14 data, that I'm aware of, that gives me any insight as  
15 to whether the dose response differs in someone who  
16 begins with a BNP level of 50, versus someone who  
17 begins with a BNP level of several hundred, you are  
18 going to be on a totally different portion of the  
19 pharmacokinetic dose response curve.

20 And I don't see any of those data here.  
21 And, in fact, when one looks at the data, there is not  
22 a convincing dose response to the infusion rate, and

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1 it would trouble me in terms of deciding how to  
2 administer it.

3 Now, when we give nitroglycerin, or sodium  
4 nitroprusside, which are very effective and potent  
5 agents, we titrate them very carefully, and we use if  
6 we have invasive monitoring, we use the wedge pressure  
7 as a goal, and if we have, we don't have invasive  
8 monitoring, we use blood pressure as a goal, and we  
9 titrate until the blood pressure gets to an  
10 unacceptable level, and it is a very comfortable way  
11 for physicians to administer a potent vasodilator and  
12 achieve the reduction in wedge pressure with safety.

13 Now, this is a whole different ballgame.  
14 We are beginning with a dose which as Dan pointed out,  
15 may be close to the top of the dose response curve.  
16 We are beginning with the same dose, and people who  
17 have a baseline BNP of 50, and those who begin with  
18 700, so they are probably a different kettle of fish,  
19 and we don't really know how to deal with that.

20 And we can't comfortably determine that if  
21 are unhappy with the response at .015, that we should  
22 then go to .03, because we aren't really sure we are

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1 going to get an added effect. In fact, that has never  
2 been the design of the studies, they were done with  
3 dose finding, and not with dose titration.

4 So I think there is some serious  
5 limitations in the data base, fascinating as this  
6 agent is, which makes it very difficult for me to  
7 write a prescription as to how to give the drug, and  
8 how to monitor the response, and how to assure safety,  
9 and how to choose the patients who should get it, and  
10 it just leaves me feeling that we don't know enough  
11 about what the drug does to sodium excretion.

12 I mean, it lowers out aldosterone levels,  
13 but we don't know anything about what that may help  
14 preserve potassium, because we don't have sodium  
15 potassium data, and it is a very difficult group to  
16 get it in.

17 So I recognize the sponsor's problem in  
18 trying to quantitate this sort of thing in a very sick  
19 population. But these are some of the theoretical  
20 benefits. The document suggests that you can get this  
21 lowering of wedge pressure without an increase in  
22 heart rate, which makes this a very attractive drug.

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1 But nitrates and nitroprusside don't raise heart rate  
2 either.

3 So those vasodilators which are standard  
4 therapy are not associated with tachycardia, and not  
5 associated with rises in norepinephrine, so that we  
6 don't really have a clear distinction between this  
7 drug and other therapies that can be utilized.

8 And we have a bit of a problem in that the  
9 traditional way to administer these drugs with  
10 titration up to desirable effect does not pertain  
11 here, and we are now facing a whole different way of  
12 administering a vasodilator drug without the ability  
13 to titrate.

14 So these are some of my concerns with what  
15 otherwise is a very attractive agents.

16 CHAIRMAN PACKER: Let me see if we can get  
17 some clarification. Ray, I'm going to ask you to help  
18 us on this.

19 There has been a distinction drawn in the  
20 past in the evaluation of drugs for heart failure,  
21 between how IV drugs are thought about, and how oral  
22 drugs are thought about. It is not uncommon in -- and

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1 there has been an evolution of thought in the past  
2 decade, that much of oral therapy has been driven by  
3 an effect on clinical status, or clinical events.

4 And although there may or may not be dose  
5 response data for oral, there is generally a concept  
6 of titration to target dose, which dominates the oral  
7 field, largely because the large scale clinical trials  
8 looking at clinical events did that.

9 The thinking that has dominated IV drug  
10 therapy for heart failure, and I think you made this  
11 point a year ago, was that if one could show a dose  
12 response relationship for hemodynamics then one could  
13 write labeling for a drug because knowing that allowed  
14 someone to tell physicians how to use a drug in  
15 accordance to the way they would normally use the  
16 drug.

17 Now, in all other case of drugs for IV use  
18 for heart failure, and maybe for many other conditions  
19 as well, cardiovascular conditions, there has been a  
20 relationship between dose and -- there is always a  
21 relationship between dose and response, but the doses  
22 explored have included a range of doses which have

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1 exhibited a range of effects.

2 On the package in front of us today  
3 suggest that there is one or maybe two doses that have  
4 a pharmacological action which is deemed desirable,  
5 not necessarily a dose response, because they may have  
6 been at the flat part of the dose response  
7 relationship, and clearly no dose response  
8 relationship for symptoms or whatever, there are no  
9 clinical events to analyze that are meaningful.

10 So the philosophy here is more like an  
11 oral than an IV agent, even though the administration  
12 of this drug is IV. And if -- but physicians still  
13 practice medicine in a dose response world, which I  
14 think is what Jay is referring to.

15 The previous guidance was dose response.

16 DR. LIPICKY: You are asking me a  
17 question?

18 CHAIRMAN PACKER: Yes.

19 DR. LIPICKY: Let me respond. Everything  
20 you said is correct, okay? But it is going to take a  
21 little while for me to respond, and it should take me  
22 very long to respond, because the concepts involved

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1 are very difficult.

2           Probably the place to start is with dose  
3 response. I disagree that there is no dose response  
4 in this data. Clearly the two doses studied changed  
5 things compared to placebo, and the stuff was there  
6 before. So you actually have three data points that  
7 you can look at, all right?

8           And the dose response is somewhere between  
9 what the basal level was, and what these two doses  
10 produced.

11           So, indeed, the interpretation that you  
12 may be near the top is correct, if your model says  
13 that there is a continuous relationship between plasma  
14 concentration and effect, with some lag.

15           And so the EC50 is somewhere down below  
16 either of the doses that were shown in these trials.

17           We will go back and look at the other  
18 trials to see if we can reconstruct some kind of  
19 conglomerate dose response. That was an error, I  
20 think, on our part for not doing that before, because  
21 I would function from the vantage point that there is  
22 a continuous dose response relationship, and this just

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1 represents one end, with the limit being hypotension.

2 And we ask people to get to the limit and  
3 so then the idea was, let's back off from that limit  
4 a little bit.

5 Now, so first there is a dose response  
6 here. Second, the notion that in chronic heart  
7 failure one should titrate to maximum dose, is an  
8 artifact of the number of dollars people are willing  
9 to invest in a chronic heart failure program.

10 They are not willing to invest finding  
11 what happens at each dose. But will invest in saying  
12 let's find the biggest dose we can use, and get away  
13 with, and compare that to placebo. That is not  
14 science, it is not anything else, it is just strict  
15 dollars.

16 What people think, and in fact anoximone,  
17 for example, is being currently worked up at a very  
18 much lower dose than at any of the doses in other  
19 trials, with the notion being that big doses of  
20 inotropes kill you, and the doses that you need are  
21 much smaller, and they will help.

22 So there is a real defect in this titrated

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1 business. The next part of the same business dose  
2 response was that if you went around the table and  
3 asked people if one had really characterized the dose  
4 response for any one drug. I don't care what drug it  
5 is, or what condition you want to use it in.

6 And you said, what dose would you start  
7 with? Some people would say, probably somewhere  
8 around the ED10 or ED20, and then titrate from there.

9 Some would say, I wouldn't start any lower  
10 than ED50, why would I want less than half the people  
11 I treat to have some response? Others would say, I  
12 use the ED90, first dose.

13 And some of those considerations would  
14 depend in part on what the adverse effects were, and  
15 how the adverse effects related as a function of dose.

16 So then the next concept is that when you  
17 vary doses by a factor of two, I'm supposed anybody  
18 ever finds a difference in anything, okay? It is  
19 almost certainly log plasma concentration, for any  
20 effector, and you vary the dose by a factor of two,  
21 your N has to really be large to find a difference in  
22 biological response.

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1           So the fact that people don't find  
2 differences in biological response with factors never  
3 surprises me.

4           Now, so I think everything you've said is  
5 right, it just, from my vantage point, this drug has  
6 a dose response relationship, it has been fairly  
7 reasonably described. The trouble is it hasn't  
8 studied a dose in empirical trials that will allow one  
9 to say, I know what dose is the smallest dose I would  
10 use. Pretty well characterized what the largest dose  
11 would be.

12           CHAIRMAN PACKER: Dan actually emphasized  
13 that point before.

14           DR. LIPICKY: I understand. Then the  
15 other part of the thing you were talking about, and  
16 I'm not sure I'm really being responsive, is that if  
17 there was an acute heart failure and a chronic heart  
18 failure program for any drug, the chronic heart  
19 failure program would be the thing that would  
20 probably, in some conceptual sense, identify that this  
21 is a useful agent, that would establish efficacy.

22           Then for acute heart failure, it is very

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1 easy for me to say all you have to do is find what  
2 dose you would use, and find that it is -- it does  
3 consonant things, and that it affects hemodynamics  
4 reasonably.

5 The big problem is when you have only an  
6 IV acute heart failure drug, then you don't have the  
7 long term chronic stuff to help you.

8 And then the IV has to be -- has to have  
9 a little more to carry itself, because it doesn't have  
10 this other part to help establish its efficacy.

11 Now, I don't know if I really responded  
12 the way you wanted me to, or if I got at any of the  
13 points you wanted to --

14 CHAIRMAN PACKER: What it allows us to do,  
15 I guess, tie Jay's point together with Dan's point,  
16 and just ask the Committee how concerned are they that  
17 a dose that is lower than the plateau dose that may or  
18 may not have been identified in this trial, that has  
19 not been identified here, how and the question is, is  
20 the lack of such identification meaningful in this  
21 NDA, and because it is frequently done.

22 Jay, I think in paraphrasing what you

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1 said, that usually is something that facilitates the  
2 use of a drug in an IV acute setting. We don't have  
3 that kind of dose here, it is more give this infusion,  
4 and pretty much you will get a lot of what you would  
5 expect with the drug.

6 How does this Committee think that the  
7 lack of such identification is a limitation to the  
8 present data base? I would like to hear more  
9 discussion about that.

10 DR. COHN: Let me just ask one question,  
11 first. Do we have BNP data so that one could actually  
12 analyze whether that impacts upon the dose response  
13 effect?

14 DR. GROSSBAR: As I understand it, the  
15 plasma concentrations were derived by subtracting the  
16 baseline BNP. So when you see the plasma  
17 concentration curves, they reflect the BNP level minus  
18 the baseline BNP.

19 DR. COHN: Baseline values, then, on each  
20 patient?

21 DR. GROSSBAR: On everyone.

22 DR. COHN: On everyone?

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1 DR. GROSSBAR: On everyone.

2 DR. COHN: Have you done any analysis to  
3 see whether there was an impact upon the response  
4 based upon what the baseline levels were? It seems  
5 to me it is a key issue here, because where you are  
6 dealing with an endogenous peptide --

7 DR. GROSSBAR: I'm not so sure I will  
8 concede it is a key issue, because that would make the  
9 predicate for the infusion of the drug the use of a  
10 diagnostic test that is not available.

11 DR. COHN: It is a key issue in us for  
12 understanding the drug.

13 DR. GROSSBAR: So we will tell you what we  
14 know.

15 DR. SAMBELL: I want to say, first of all,  
16 that we did actually do a concentration effect  
17 analysis after the NDA was submitted. We felt that it  
18 was an important issue, and it would help to clarify  
19 some things.

20 And maybe more so for those that believe  
21 in modeling, which I do to a certain degree.

22 And what that modeling has shown is that

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1 there is a graded concentration effect relationship in  
2 the range of concentrations seen with at least the  
3 single dose studies, and that is the data that we used  
4 for the modeling, because it gives a much broader  
5 range of concentrations.

6 There is a slight lag between the effect  
7 relative to the concentration, and my feeling from  
8 that analysis, and what is coming out of that, is that  
9 we are actually operating in more of the linear region  
10 of the dose or concentration effect, relationship if  
11 you are looking at a saturable model altogether.

12  
13 And this finding that the .015 and the .03  
14 do not differ significantly in this one study, I think  
15 is an aberration. And I would not be misled by that.  
16 I think you need to look at the whole picture.

17 The other thing that we did look at is  
18 whether there was a relationship between endogenous  
19 concentrations and the, if you will, the D50, or C50  
20 in the concentration effect relationship.

21 And there didn't seem to be any apparent  
22 relationship between that baseline and the response,

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1 although given that it is a significant issue with  
2 something that we can go back and look at further.

3 DR. COHN: Two real quick things. So this  
4 was with respect to wedge pressure?

5 DR. SAMBELL: This is with respect to  
6 pulmonary capillary wedge pressure.

7 DR. COHN: And the actual concentrations  
8 of the peptide on treatment were orders of magnitude  
9 greater than baseline, or two-fold?

10 DR. SAMBELL: The actual data that was  
11 used in the analysis was from study 309, so that was  
12 as much as 10 micrograms per kilogram given as a  
13 single bolus in actual multiple bolus.

14 DR. COHN: So plasma concentrations on  
15 treatment were orders of 2, 1, 2, 3?

16 DR. SAMBELL: Maybe 10 or more.

17 DR. COHN: Ten orders of magnitude greater  
18 than baseline?

19 DR. SAMBELL: Yes. I can give you those  
20 exact values. Tenfold.

21 DR. COHN: Tenfold?

22 DR. SAMBELL: Right.

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1 DR. COHN: So one order of magnitude.

2 DR. SAMBELL: Well, at least, it could be  
3 more than that.

4 CHAIRMAN PACKER: We should clarify one  
5 thing. I don't think anyone here is saying there  
6 isn't a relationship between dose and effect. I think  
7 that what the only thing that we are struggling with  
8 here is the pragmatic issue as to whether there is a  
9 relationship between dose effect within the  
10 recommended range.

11 If one goes to .06 or higher doses, one is  
12 going to get more of an effect, but there will be more  
13 hypotension, the sponsor is justifiably uncomfortable  
14 with that.

15 And for reasons that Ray mentioned, there  
16 is a relationship between dose and effect here. But  
17 that is to be distinguished from, I think, the issue  
18 that Jay mentioned, which is in the recommended range  
19 one is more likely than not to give, in most cases,  
20 single dose of the drug, with the expectation that  
21 there will be some predictable effects on hemodynamics  
22 and perhaps symptoms without the traditional concept

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1 of significant up and down titrations.

2 DR. LIPICKY: But it is a bit more of a  
3 problem since basically the Committee was discussing  
4 the business of what would you do if you didn't have  
5 a wedge pressure, said I don't know what to look at to  
6 tell whether people are getting better or not.

7 And so then you are sort of stuck with  
8 having some empirical information at hand that tells  
9 you what dose would be reasonable at the smallest  
10 dose, even though I can't suppose that I could have  
11 the smallest dose that has been studied, and would  
12 still have an effect, but that is probably my  
13 imagination.

14 CHAIRMAN PACKER: Marv?

15 DR. KONSTAM: I just want to actually  
16 concur that my best explanation for the specific  
17 observation with regard to the .015 and .03 doses in  
18 311 is probably, my most likely explanation would be  
19 that it is an aberration related to the .03 group, as  
20 opposed to Dan's concern that we are actually at the  
21 top of the dose curve, and the reason for my saying  
22 that is, first of all, the .06 dose within that study

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1 does have a higher wedge pressure.

2 And, furthermore, there is a dose response  
3 relationship within 325. So I think, at least my  
4 level of concern around this really relates to just  
5 how much, you know, hard data. What do we really know  
6 from 311 as opposed to what is the most likely dose  
7 response relationship here.

8 CHAIRMAN PACKER: Fine, then let's just --  
9 I think that there is general consensus amongst the  
10 Committee on 3b, which is, there is no direct  
11 comparison data on wedge pressure.

12 So let's just get a sense from the  
13 Committee, we can go around very, very quickly. Are  
14 you or are you not concerned that the sponsor has  
15 identified a dose which gives, in effect,  
16 significantly less than their starting dose?

17 In other words, how concerned are you that  
18 their initial recommended dose is close to their  
19 plateau dose in terms of the general use of the drug?  
20 It could be you are not concerned at all, it could be  
21 that you are concerned, and I think that that would  
22 epitomize some of the issues that Jay brought in, and

1 Marv, than has now commented on.

2 Because clearly, if you are not concerned,  
3 then this issue goes away. So let's start. Joann,  
4 how concerned are you that this is -- that there isn't  
5 a dose lower than the plateau dose in order to  
6 initiate therapy?

7 DR. LINDENFELD: Well, I am a little bit  
8 concerned, but I'm not terribly concerned. On the  
9 other hand I sort of like the idea that side effects  
10 are relatively low, and this is a dose to start on,  
11 and you get a definite effect, and it may decrease  
12 hospitalization, there is not multiple assessments.

13 So I'm a little bit concerned, but not  
14 terribly concerned about it.

15 CHAIRMAN PACKER: Lem?

16 DR. MOYE: It is not my greatest concern,  
17 but I am concerned.

18 CHAIRMAN PACKER: Ileana?

19 DR. PIÑA: I am somewhat concerned, not  
20 strongly concerned.

21 CHAIRMAN PACKER: Marv?

22 DR. KONSTAM: Well, I'm somewhat

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1 concerned. I think that there are a number of  
2 questions about this drug, and I think we have just  
3 one more, that in one pivotal hemodynamic trial we  
4 don't clearly see that differential that we like.

5 So I think I'm somewhat concerned.

6 CHAIRMAN PACKER: Tom?

7 DR. GRABOYS: Well, I'm concerned because  
8 I think in order for practitioners to understand how  
9 to use this drug they are going to have to have some  
10 sense of dosing. And once it is in the community,  
11 these selected adverse events, or side effects, are  
12 quite significant.

13 You are looking at 40 percent of selected  
14 adverse reaction as compared to about 20 percent for  
15 a control. So I think those numbers will probably  
16 increase. So I think that is of concern.

17 CHAIRMAN PACKER: Dan?

18 DR. RODEN: I think it is a concern, I  
19 don't think it is a necessarily a fatal or limiting  
20 concern. I think that Ray's suggestion that the  
21 Agency go back and look at the plasma concentration  
22 response data as they are being generated, and as we

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1 don't see them right now would be a reasonable way of  
2 figuring out whether a lower dose might be something  
3 to think about as the package insert is written,  
4 without data.

5 CHAIRMAN PACKER: Cindy?

6 DR. GRINES: Yes, I think it is of minimal  
7 concern to me.

8 CHAIRMAN PACKER: I'll just say I don't  
9 think it is a concern at all, only because if I have  
10 a drug that does what I -- a dose that does what I  
11 want it to do, and it is well tolerated, I don't mind  
12 that conceptual model.

13 DR. LIPICKY: You are all ED90 people?

14 CHAIRMAN PACKER: Yes, ED90 people. I  
15 never thought of myself as an ED90 person before. But  
16 we are not all ED90 people, some of us are ED50  
17 people.

18 DR. LIPICKY: There were some exceptions.

19 CHAIRMAN PACKER: How concerned, and Marv  
20 mentioned this before, the data for 24 hours, there  
21 may or may not be any attenuation at 24 hours, is  
22 literally impossible to tell.

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1           The -- maybe we should ask, is the sponsor  
2 proposing use only for 24 hours? Because that is not  
3 clear in the proposed labeling.

4           DR. GROSSBAR: In the question, the final  
5 question Dr. Lipicky asked, define acute treatment as  
6 less than 24 hours. The sponsor was less specific,  
7 and hoped to gain labeling similar to that which is  
8 used for other products in this indication, which is  
9 not terribly specific about duration of therapy.

10           CHAIRMAN PACKER: Okay. Taking -- let's  
11 assume for a moment, because otherwise it makes  
12 discussion unbelievably complicated, the labeling, as  
13 one of the latter questions indicates, question number  
14 12 indicates to be specific for 24 hours.

15           How concerned are you about the potential  
16 for attenuation? And let me just suggest, to  
17 facilitate discussion, you may be not concerned at  
18 all, given the data, if in fact the drug would be used  
19 for 24 hours because you've got data to 24 hours.

20           You may say that you don't know much  
21 beyond 24 hours, and you wouldn't want to suggest that  
22 there are data, or that the drug would be recommended

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1 for use beyond 24 hours. That would be a very empiric  
2 approach.

3 The question is, does the Committee agree  
4 with that empiric approach? Marv?

5 DR. KONSTAM: No matter what the labeling  
6 is, this drug, if approved, will be used far longer  
7 than 24 hours.

8 CHAIRMAN PACKER: That doesn't matter,  
9 because it is like the acute MIs discussion. The  
10 question is, do you want the labeling to reflect that?

11 DR. KONSTAM: I think it is a little --  
12 not perfectly analogous with acute MI discussion, but  
13 the --

14 CHAIRMAN PACKER: Do you want the labeling  
15 to reflect that?

16 DR. LIPICKY: You are asking whether  
17 people are comfortable that the effects last for 24  
18 hours?

19 CHAIRMAN PACKER: We are addressing the  
20 question about attenuation, does this effect last  
21 during continuing administration.

22 DR. LIPICKY: And you chose to limit it to

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1 the --

2 CHAIRMAN PACKER: One needs to define what  
3 that time frame is in order to answer the question.

4 DR. LIPICKY: Right.

5 CHAIRMAN PACKER: We can't define that  
6 time frame beyond 24 hours. And there is a -- if  
7 there is evidence for attenuation before it may become  
8 more marked after.

9 DR. LIPICKY: Right. But the question you  
10 asked Marvin was for 24 hours will the effect be --

11 CHAIRMAN PACKER: That is right.

12 DR. LIPICKY: And that is the only  
13 question you have to answer now.

14 DR. KONSTAM: I'm sorry, what is my  
15 question?

16 CHAIRMAN PACKER: Is there an effect for  
17 24 hours?

18 DR. LIPICKY: Will the effect you get last  
19 for 24 hours.

20 DR. KONSTAM: Yes. Well, we have an  
21 effect for 24 hours, there may be some attenuation.

22 CHAIRMAN PACKER: Does anyone disagree?

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1 (No response.)

2 CHAIRMAN PACKER: Let's go to question 4,  
3 it is exactly the same principle, the difference here  
4 is the hemodynamic variable is different, and let me  
5 just, for the sake of time and clarity, say that this  
6 can apply to all other hemodynamic variables that you  
7 think are important, other than just cardiac output.

8 Marv?

9 DR. KONSTAM: Yes, I think the answers are  
10 identical for those for the wedge pressure.

11 CHAIRMAN PACKER: And you are not  
12 concerned that statistical significance was not  
13 reached on these other variables in the only study  
14 that looked at them at 24 hours?

15 DR. KONSTAM: Which parameters are you  
16 talking about?

17 CHAIRMAN PACKER: Cardiac output, right  
18 atrial pressure, systemic vas resistant, all of them  
19 were no longer statistically significant at 24 hours  
20 in the only study that looked at it.

21 You may not be worried about it, I just  
22 want to know whether --

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1 DR. KONSTAM: Well, I would have to go --  
2 my general sense, having looked at the data.

3 DR. LIPICKY: He just gave you a new fact.

4 DR. KONSTAM: Yes, I missed that fact, to  
5 tell you the truth, about the loss of statistical  
6 significance at 24 hours.

7 DR. LIPICKY: You just knocked something  
8 new in, though.

9 CHAIRMAN PACKER: No, that was mentioned  
10 by the sponsor in their presentation.

11 DR. GRINES: It is slide 21, although the  
12 relative effect looks pretty similar, there is no  
13 longer statistically significant, and it is due to  
14 variation.

15 CHAIRMAN PACKER: Yes, the P values  
16 actually are in the document, that in study 311 there  
17 is an effect compared with placebo at pulmonary wedge  
18 pressure at 24 hours, but not for the other  
19 hemodynamic variables.

20 As Cindy has emphasized, the dose response  
21 relationship is still there if, you know, in other  
22 words relationship between -- I hate to use that

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1 because we just discussed -- the relationship amongst  
2 doses is still there. But none of those effects are  
3 statistically significant.

4 I believe I'm saying, correctly, for any  
5 variables other than wedge pressure. I don't know if  
6 that is a true statement.

7 DR. KONSTAM: Let me just -- I'm not sure  
8 whether the P values at 24 hours are really the  
9 critical question, quite frankly.

10 I think, and maybe we will have to call on  
11 Lem on this, but let me just give you a sense of the  
12 answer to this question. I think the drug has a  
13 beneficial effect on all of these hemodynamic  
14 parameters. I think that is my conclusion from  
15 looking at all of the data.

16 And I think that my sense of it, looking  
17 at all of the data, is that there is a continued  
18 effect on 24 hours, regardless of what the particular  
19 P value happens to be at that point, that is my  
20 opinion, looking at all the data.

21 I do think there is evidence for some loss  
22 of effect. So I guess my answer is, now that you

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1 pointed out to me, I'm not overly concerned, per se,  
2 about the fact that P values disappear at 24 hours.

3 CHAIRMAN PACKER: Okay. Any general  
4 discussion before we go around and just get the  
5 consensus?

6 (No response.)

7 CHAIRMAN PACKER: Well, why don't we start  
8 the same way. Joann, basically do you agree or  
9 disagree? The issues here don't relate to minimum  
10 dose, they more relate to more persistence of the  
11 effect.

12 DR. LINDENFELD: I think there is  
13 persistence of effect.

14 CHAIRMAN PACKER: Lem?

15 DR. MOYE: It is my pleasure to agree with  
16 Marv.

17 CHAIRMAN PACKER: To?

18 DR. MOYE: To agree with Marv.

19 CHAIRMAN PACKER: He agrees with you?

20 DR. RODEN: I'm shocked.

21 DR. MOYE: If you want me to talk for a  
22 couple of minutes about P values here?

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1 (General laughter.)

2 DR. MOYE: I have a few brief remarks  
3 here.

4 CHAIRMAN PACKER: Ileana?

5 DR. PIÑA: I agree.

6 CHAIRMAN PACKER: Tom?

7 DR. GRABOYS: I agree. I agree that the  
8 effect is preserved, but there is no dose response in  
9 that effect.

10 CHAIRMAN PACKER: Okay. Cindy?

11 DR. GRINES: I agree.

12 CHAIRMAN PACKER: I agree, as well. It is  
13 exactly the same situation with respect to symptoms.  
14 The issues are similar, the -- it is three separate  
15 questions. The only question that is -- forget about  
16 5c, the questions are one, is there an effect on  
17 symptoms; two, is there a relationship between effect  
18 and dose? Three, how long does the effect last? And  
19 four, how does it compare to conventional therapy.

20 Marv?

21 DR. KONSTAM: I actually think that some  
22 of the issues here are different. And so let me just

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1 preface the answer here by saying my own view about  
2 this, as I said earlier, is that I'm looking here for  
3 confirmation that the effect on wedge is clinically  
4 relevant, rather than looking at it as a -- you know,  
5 as a necessary isolated finding for approvability's  
6 sake, but rather confirmation of the clinical  
7 relevance to the wedge pressure reductions.

8 So let me just start with that. I think  
9 that there are a lot of problems with the symptom  
10 data, and we've really dwelled on those. I think they  
11 could be done better in the future, but now we are  
12 left with this data set.

13 Presented with this data set, I do  
14 believe, looking at it through the issues, there still  
15 is a demonstrable effect on symptomatology. And,  
16 actually there appears, to the extent that we accept  
17 that, there actually appears to be a dose response in  
18 study 325. So I guess that is one set of answers.

19 In terms of assuming that that is correct,  
20 how long it lasts, that becomes a little confusing.  
21 So we don't have a placebo control at 24 hours. We  
22 have, in study 325, after six hours the drug therapy

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1 is opened up, and so we have it compared to what is  
2 called conventional care.

3 And there we do not have any significant  
4 differences across, from between standard care and  
5 drugs, an active drug at 24 hours, although the  
6 apparent improvement that we saw in 6 hours, in the  
7 Nesiritide groups appears to be sustained.

8 So you can interpret that in a few  
9 different ways. You can say, well I think that we  
10 actually have made patients better, and they probably  
11 are still better at 24 hours.

12 Or you can say, well you know, this drug  
13 really didn't do any better than if I didn't have it.  
14 And actually there is a trend at 24 hours toward it  
15 being a little bit worse than standard care, but that  
16 may be related to a lag in getting certain other kinds  
17 of therapies going.

18 So we are left a little bit unsure about  
19 what -- I mean, I think the 24 hour data are there,  
20 but I think that they are open for those sorts of  
21 interpretation.

22 CHAIRMAN PACKER: Marv, just taking off on

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1 what you said there, I guess there are three ways of  
2 looking at the symptom data.

3 One, they are terribly flawed, and one  
4 can't interpret anything. Two is that they are  
5 sufficiently flawed that one can gain comfort about  
6 the meaningful of the hemodynamics, but not  
7 sufficiently comfortable to provide a claim.

8 Because the sponsor is asking for a claim.

9 DR. KONSTAM: Related to symptom  
10 improvement?

11 CHAIRMAN PACKER: Yes. It says, proposed  
12 indication statement, sorry to keep on referring to  
13 this, it also causes rapid symptomatic improvement.

14 And the third possibility is to say both  
15 your comfort level with hemodynamics and the claim is  
16 acceptable.

17 So I'm sure there are all sorts of levels  
18 of comfort in between those two, but just to make it  
19 very, very straightforward, one is a claim, the  
20 sponsor would like that claim; two, it is good enough  
21 to give one comfort about hemodynamics but not good  
22 enough for a claim; and three, it is not good enough

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1 for either.

2 And I think that it will allow us to  
3 sharpen our thinking very well if we can define the  
4 level of comfort and if we can do that, then a lot of  
5 things fall into place. Is that fair?

6 DR. KONSTAM: Yes, I think that is good.  
7 And I would say, somewhere around level 2 is where I'm  
8 at.

9 CHAIRMAN PACKER: Level two is comfort  
10 that the hemodynamics are meaningful, but not enough  
11 for a claim?

12 DR. KONSTAM: Right, but let me, since  
13 this is a new question for me, let me ponder it for a  
14 second. You know, I think that is right, based on  
15 everything that we said.

16 However, I would just make a distinction.  
17 Based on what I've seen I wouldn't mind, assuming the  
18 drug were approved, seeing that reported in the packet  
19 insert, that these observations were found as opposed  
20 to the claim per se.

21 CHAIRMAN PACKER: I guess that is a sort  
22 of -- it is subgroup of A?

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1 DR. KONSTAM: Right.

2 CHAIRMAN PACKER: Okay, fine.

3 DR. LIPICKY: Those one, twos, and threes  
4 were real numbers, not integer numbers.

5 DR. KONSTAM: Yes, 2.2.

6 CHAIRMAN PACKER: Okay, does everyone  
7 understand the options? The options are: One, it is  
8 good enough for a claim; Two, it is good enough for a  
9 comfort level for hemodynamics; Three, it is not good  
10 for either. And Two-two comfort level for  
11 hemodynamics.

12 DR. GRABOYS: A good comfort level, not a  
13 claim.

14 DR. RODEN: Two.

15 CHAIRMAN PACKER: Cindy?

16 DR. GRINES: Repeat the question?

17 CHAIRMAN PACKER: Yes. Are the data on  
18 symptoms in your view good enough for a claim, because  
19 that is what the sponsor is asking for; good enough to  
20 give you comfort that the hemodynamic changes are  
21 clinically -- maybe clinically meaningful, or three,  
22 are they good enough for a neither?

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1 DR. GRINES: I think it is good nough for  
2 a claim.

3 CHAIRMAN PACKER: Joann?

4 DR. LINDENFELD: I think 2.

5 CHAIRMAN PACKER: Lem?

6 DR. MOYE: Three.

7 DR. PIÑA: Two.

8 CHAIRMAN PACKER: I would vote three,  
9 actually. So that, in fact, it is one 1, two 3s, and  
10 the rest 2s, the 2 is the majority. Cindy was one.

11 DR. LIPICKY: One was it was no good for  
12 nothing?

13 CHAIRMAN PACKER: No one is good enough  
14 for a claim.

15 DR. LIPICKY: Three is it was not good for  
16 nothing?

17 CHAIRMAN PACKER: Right. Well, we didn't  
18 say good enough for nothing, we said neither.

19 DR. LIPICKY: Right. Are you sure you  
20 have that, Joan?

21 SECRETARY STANDAERT: Yes.

22 DR. LIPICKY: Okay.

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1                   CHAIRMAN PACKER:    The Committee, the  
2                   consensus of the Committee is that it is good enough  
3                   for a comfort level that the hemodynamics are  
4                   meaningful, clinically meaningful.    That is the  
5                   consensus for you.

6                   And in terms of persistence effect, and  
7                   comparability of the effect, right now the data, as  
8                   Marv has summarized it, the data are placebo  
9                   controlled.    Actually, we don't necessarily have to  
10                  tackle all of that, since we now have answered two, is  
11                  that right?

12                  That solved that problem.    Okay, good.

13                  Six, at the beginning of the drug infusion  
14                  what is the time course of the onset of effect, what  
15                  is the time course of the offset of effect?    Are the  
16                  time courses similar for the beneficial and adverse  
17                  effects?    Are the data as to the time course that  
18                  changes the effect after changes in the infusion rate.

19                  Marv?

20                  DR. KONSTAM:    Yes.    I think the time to,  
21                  I think it is measured in hours.    I'm looking at a  
22                  graph on page 47 of the medical review, which

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1 basically shows that in -- that the maximum effect,  
2 maximum wedge pressure effect is showing up in the  
3 three to four hour range, following initiation of  
4 infusion.

5 And that the time to offset similarly,  
6 from what I can see, is hours, maybe a couple of hours  
7 to the elimination of the effect.

8 I think that we really -- this is a  
9 concern, that we don't really know whether these time  
10 courses are similar for the beneficial or adverse  
11 effects.

12 I mean, I guess the adverse effect for  
13 which this makes some sense is the hypotension. And  
14 I've raised that concern, that we don't have -- I  
15 don't have a clear sense of what happens to blood  
16 pressure after we stop it.

17 I get the sense, from the data that was  
18 mentioned that, again, it is of the order of a couple  
19 of hours before the hypotensive effect is off.

20 So we don't have any data here about the  
21 time course of the change of effect after change in  
22 infusion rate.

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1 CHAIRMAN PACKER: So the onset of the  
2 effect is within hours the time courses of whether or  
3 not there is a tracking of the beneficial and adverse  
4 effects is unclear but likely?

5 DR. KONSTAM: Okay, unclear but likely.

6 CHAIRMAN PACKER: Unclear but likely is,  
7 I think, an accurate description of the data, no?  
8 Right?

9 DR. RODEN: That is for blood pressure?

10 CHAIRMAN PACKER: Yes.

11 DR. RODEN: But for creatinine --

12 CHAIRMAN PACKER: Right, for creatinine we  
13 don't know.

14 I get the impression that a lot of this is  
15 focused on adverse hemodynamic as opposed to adverse  
16 laboratory, because adverse laboratory doesn't really  
17 have a time constant. Isn't that right?

18 DR. LIPICKY: Well, it was mainly for the  
19 continuous things that are measured frequently,  
20 because in fact the laboratory was measured like once  
21 a day, or once every other day, and it is hard to  
22 describe its time constants.

1                   CHAIRMAN PACKER: Anyway, I think Marvin  
2                   has basically described it. Are there any  
3                   disagreements? Dan?

4                   DR. RODEN: I'm still troubled and struck  
5                   by the fact that the wedge pressure changes occur over  
6                   three to four hours, but the cardiac index changes in  
7                   both the pivotal studies occur at the first time  
8                   point.

9                   And so I come back to the issue of boluses  
10                  versus infusions, of multiple pharmacologic effects.  
11                  So I would sort of modify my answers a little bit, but  
12                  otherwise I agree with Marv.

13                  CHAIRMAN PACKER: Okay. Let's move on to  
14                  7. What is known about the co-administration of the  
15                  drug with other vasodilators? Marv.

16                  DR. KONSTAM: Well, really very little.  
17                  I think the only information we have at all about this  
18                  is from study 325, after the six hour timepoint when  
19                  the patients were opened to receive whatever therapy.

20                  And we have some descriptions of what  
21                  happened to that population, but really nothing  
22                  systematic. There were a variety of different agents

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1 used, and it really isn't, it isn't enough to know  
2 what effect this agent has on top of -- on top of  
3 other such agents.

4 CHAIRMAN PACKER: Jay?

5 DR. COHN: We did see some data on the co-  
6 administration of ace inhibitors, which was a little  
7 bit disturbing. And of course ace inhibitors  
8 stimulate kinanes and increase nitric oxide levels,  
9 and stimulate cyclic G, so there may be some dual  
10 mechanism here that we have to pay attention to.

11 I guess the same thing would be true with  
12 a nitrate, and there is a lot of data with patients  
13 who are taking oral nitrates. And, once again, I  
14 don't know whether this drug will have a greater  
15 effect in patients on nitrates, or with co-  
16 administration of nitroglycerin, and I think that is  
17 something that we certainly should know.

18 I guess to go beyond the vasodilator I  
19 think there is a concern about what the drug does to  
20 co-administration of a loop diuretic. Do we have any  
21 data to tell us whether there is any interference  
22 with, or augmentation of, the loop diuretic effect.

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1           These are the sorts of things that would  
2           have to be done not in phase III studies, but really  
3           back in phase II, to really do some drug/drug  
4           interaction studies. Maybe they have been done. But  
5           I feel, on the basis of the data that I've looked at,  
6           that I'm a little insecure about how this vasodilator  
7           mechanism interacts with diuretics and with other  
8           vasodilators and whether that should be an important  
9           consideration.

10           DR. KONSTAM: Can I just follow up on  
11           that? I mean, that is a very good point, and we saw  
12           something that Ray's concern, it is going to come back  
13           at us when we are talking about adverse effects.

14           But as Jay points out we do have some data  
15           about concomitant administration of ace inhibitors,  
16           and it is concerning data because, in fact, the  
17           incidence of adverse hypotension was highest in the  
18           group with the ace inhibitors, and there was a chunk  
19           of patients not on ace inhibitors.

20           So, in fact, that particular adverse  
21           effect may be more prevalent in a population more  
22           uniformly treated with ace inhibitors.

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1 DR. GROSSBAR: We actually did a specific  
2 study similar to what Dr. Cohn was suggesting with ace  
3 inhibitors in phase II, which compared the  
4 interaction, specifically of BNP with ace inhibitors,  
5 because there had been a pre-clinical study suggesting  
6 that ace inhibitors inhibited metabolic clearance of  
7 BNP that was a factor in it.

8 We went to a lot of effort, actually, to  
9 replicate that and proved that that is not the case.  
10 And when we did the interaction study in phase II, and  
11 it was a substantial one, we found absolutely no  
12 interaction between BNP and ace inhibitors given as a  
13 bolus, I want to qualify that, we used different bolus  
14 doses of BNP, looked at ace inhibitors, plasma  
15 concentrations, and other side effects.

16 The reason we didn't make much of that in  
17 the presentation is because we recognized that someone  
18 could likely come back and say that a narrow clinical  
19 pharmacology study like that doesn't really represent  
20 what happens when patients are running amok coming  
21 into the hospital.

22 So in a sense I would challenge that you

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1 could go back and do an interaction study with a loop  
2 diuretic. You might be able to show some interesting  
3 effect on renal function one way or another.

4 But you would still, in the end, be left  
5 with the clinical results that we presented in the  
6 large trials, where there was a lot of diuretic use.

7 DR. COHN: How do you relate that  
8 experience with the ace inhibitor with the apparent  
9 dramatic efficacy of Nep base inhibitors, which should  
10 really combine the effects of a peptide --

11 DR. GROSSBAR: Are they approved  
12 therapies?

13 DR. COHN: No, but they, you know, there  
14 are some --

15 DR. GROSSBAR: Well, we have to wait until  
16 the FDA has had a chance to adequately review that  
17 data.

18 DR. COHN: Okay, but I'm just asking you  
19 your opinion. I mean, those two drugs seem to be  
20 interactive, at least from published data.

21 DR. GROSSBAR: I can only report what we  
22 did and what we saw.

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1 DR. PIÑA: I am sorry, was that your study  
2 310?

3 DR. GROSSBAR: 310 and 309. 309 was done  
4 without ace inhibitors, and 309 was --

5 DR. PIÑA: And an --

6 DR. GROSSBAR: Right. Some people got,  
7 you know, but generally it was an aliquot.

8 CHAIRMAN PACKER: Ray are you happy with  
9 the discussion that is taking place on question 7,  
10 because clearly you are looking for specific opinions  
11 and guidance from the committee here.

12 Are you satisfied, can we go on to 8?

13 DR. LIPICKY: You may go on to 8, but I  
14 must admit that I don't know what to do with your  
15 discussion. I have listened to it, but it isn't  
16 clear to me exactly what action to take as a  
17 consequence of it.

18 CHAIRMAN PACKER: Dr. Karkowsky?

19 DR. KARKOWSKY: The question I had more  
20 was there is two ways to put two things together, one  
21 to start with this drug, and add something to it,  
22 which as you have a little experience in this data

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1 base.

2 The other thing is to put this drug onto  
3 something else. If you are titrating somebody and get  
4 an optimum dose of a good drug, let's say a  
5 vasodilator or an inotrope, and then you have this  
6 drug which is not easily titratable, what would be  
7 your outcome, how would you say to use it?

8 CHAIRMAN PACKER: Okay, I got it. So the  
9 question that might -- another way of formulating the  
10 question, because the question in 7 was how; and maybe  
11 what we should do is have more of a definitive way of  
12 phrasing this question.

13 What should the labeling of this drug say,  
14 if any, about whether this drug should be used alone  
15 or in combination with other IV drugs for the  
16 treatment of heart failure? Drugs with vasodilator --  
17 doesn't even have to be IV, it could be oral drugs as  
18 vasodilators.

19 DR. LIPICKY: Well, other oral drugs were  
20 used in combination with, in the trials.

21 CHAIRMAN PACKER: Yes, right, so the  
22 question --

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1 DR. LIPICKY: And the --

2 CHAIRMAN PACKER: So you want the question  
3 to be IV?

4 DR. LIPICKY: I hear people's reservations  
5 with respect to how much specific information there  
6 is, and whether things can get dissected out. And, in  
7 fact, we didn't see a lot about whether responses were  
8 different in people with different drugs on board.

9 And my problem is I don't know what to do  
10 with that, except note it. And I don't know that one  
11 would want to translate that into specifying some  
12 action that others should take on the basis of that  
13 deficiency, if in fact you should ignore that  
14 deficiency and recommend approval.

15 DR. GRABOYS: How can you say anything but  
16 that experience is limited with concomitant use of --

17 DR. LIPICKY: Well, that is not saying  
18 anything.

19 DR. GRABOYS: -- and that is what you have  
20 -- that has to be commented on.

21 DR. LIPICKY: But that is easy to say, I  
22 heard the discussion that it is easy to say. But that

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1 doesn't say anything, that is like saying, drive  
2 carefully.

3 DR. GRABOYS: Well, you put signs up that  
4 says drive carefully.

5 DR. PIÑA: That is good advice, though.

6 DR. LIPICKY: It is good advice, but it  
7 doesn't say anything.

8 DR. GRABOYS: Why is this complicated?

9 CHAIRMAN PACKER: Ray, just picking up on  
10 what Tom has said, is there a problem with saying  
11 drive carefully if you --

12 DR. LIPICKY: No.

13 CHAIRMAN PACKER: -- don't know any  
14 better?

15 DR. LIPICKY: No, I'm happy to do that,  
16 but I think if you keep going you will want me to say  
17 more.

18 DR. COHN: I think the message that you've  
19 gotten, Ray, is that there is a deficiency in the data  
20 base, and the question as to whether that deficiency  
21 in the data base should influence the approval process  
22 would relate to many other things in the data base

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1 that may be so powerful that you are willing to  
2 exclude that.

3 On the other hand, if the rest of the data  
4 base wasn't very powerful, you might find that this  
5 deficiency was an overwhelming fatal flaw.

6 DR. LIPICKY: And that is correct, and  
7 that is why there is an order to the questions, and  
8 approval will come down below where all of these  
9 things you ought to be noting in your head.

10 CHAIRMAN PACKER: But I don't get the  
11 sense that anyone in this room would think that if a  
12 patient was already on an IV vasodilator, I hope I'm  
13 saying this correctly.

14 That the IV vasodilator should be  
15 withdrawn when treatment with this drug is initiated.  
16 I don't think I'm hearing anyone say that. What  
17 should a physician do?

18 I didn't think anyone would say that, but  
19 now looking around the room I don't know what people  
20 are thinking.

21 DR. RODEN: Or lasix, worse yet.

22 DR. GRINES: Well, at least there is data

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1 on administration of diuretics during the treatment  
2 period. But I'm not sure that there was any IV  
3 vasodilators given.

4 CHAIRMAN PACKER: Well, let me see if I  
5 understand. Let me make sure. If someone is on IV  
6 nitroglycerin, or you can make -- substitute any drug,  
7 someone is on something, what -- I hope -- well, let  
8 me try to phrase this in a more detailed fashion.

9 What guidance should be presented tot he  
10 practicing physician as to what people should do with  
11 concomitant therapy, be it oral or IV, when this drug  
12 is administered.

13 And that is the two-tailed generic  
14 question. I didn't think I heard anyone, but Abe's  
15 question is right to the point. I didn't think I  
16 heard anyone say that they thought that some drugs  
17 should be withdrawn before this drug is administered,  
18 but maybe that is -- maybe I'm being presumptuous  
19 here.

20 So let me see if I can get a  
21 clarification. Would someone help to clarify what the  
22 Committee's position is on concomitant therapy, and

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1 what should be either done with this drug, or done  
2 with a concomitant therapy?

3 Because Doctor Karkowsky's point is, gee,  
4 there wasn't a whole lot of concomitant therapy,  
5 normally one would adjust the dose if someone was  
6 hyper responsive, but here there is -- we don't have  
7 a whole lot of experience with a variety of doses.  
8 Ray has to write labeling.

9 What can we do? We'll go. Marv and  
10 Ileana.

11 DR. KONSTAM: Well, I'm not sure, but I  
12 think one could make a case for making concomitant use  
13 of other intravenous vasodilators contraindicated.  
14 And let's see why I would say that.

15 Well, first of all, there is no data to  
16 support the safety of concomitant use. The safety  
17 concerns that we have about this agent, a part of that  
18 relates to the hypotensive potential of the agent.

19 We have said that the rate of offset of  
20 vasodilator effect, or hypotensive effect of this  
21 agent is not immediate. And let's couple that with  
22 asking ourselves the question, what is the physiologic

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1 rationale for combining this agent with other  
2 intravenous vasodilator agents.

3 So I'm sort of working up to it, but I  
4 think you could take that and make a case to say other  
5 IV vasodilator agents at this point should be  
6 contraindicated, concomitantly with this agent.

7 CHAIRMAN PACKER: Ileana?

8 DR. PIÑA: I think you have to say what  
9 was done here. There were other agents, were  
10 withdrawn prior to the initiation of this drug. And  
11 what happens with the two together is uncertain.

12 Now, I also think that you can go on and  
13 say that in 326 a whole series of patients were on  
14 other concomitant medications, so that -- but that is  
15 on the long term effect. But at the acute  
16 administration the patients had been taken off other  
17 drugs for a certain number of hours.

18 So that if you have to get a decay of  
19 blood level it is gone. So I would assume that  
20 whatever was hanging around was gone.

21 CHAIRMAN PACKER: I hear what everyone is  
22 saying. I'm a little bit surprised. I guess this may

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1 be a side effect of living in an ED90 universe.

2 DR. LIPICKY: Yes, because no one would  
3 have any concern if you start at the ED10.

4 CHAIRMAN PACKER: Right, there would be --  
5 if we lived in an ED10 universe, then none of these  
6 issues would exist. But because we live in the ED90  
7 universe they do.

8 DR. LIPICKY: You have a problem.

9 CHAIRMAN PACKER: There is a price to be  
10 paid for living in an ED90 universe.

11 Let me just make sure that I understand.  
12 Would it be the Committee view that this drug should  
13 not be given, that the labeling should, in fact, make  
14 clear that this drug should not be given together with  
15 other IV vasodilators or other drugs with vasodilator  
16 IV vasodilator properties?

17 I'm just trying to -- in other words,  
18 should the package insert reflect what was done in the  
19 clinical trials in terms of the withdrawal of the  
20 drug? Tom?

21 DR. GRABOYS: Yes. I mean, you've  
22 articulated it very well.

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1 DR. RODEN: I agree. I mean the concern  
2 is the hypotension, and any additional IV inotrope, or  
3 IV therapy would I think exacerbate that, and there is  
4 no data, so I think the package insert should say,  
5 should perhaps go so far as to say until other data  
6 are available. It is contraindicated, which is a  
7 little  
8 different from saying not do it.

9 CHAIRMAN PACKER: Joann?

10 DR. LINDENFELD: I agree. At least IV  
11 vasodilator I think should be strongly discouraged, if  
12 not contraindicated.

13 CHAIRMAN PACKER: And I guess I imagine  
14 that must apply to ace inhibitors, since they have big  
15 time vasodilator properties. Lem?

16 DR. MOYE: Their use should be  
17 discouraged.

18 CHAIRMAN PACKER: Ileana?

19 DR. PIÑA: I agree, as stated my point.

20 CHAIRMAN PACKER: And Marv, I think you  
21 said that? Okay. I'm trying to figure out a way of  
22 voting that shouldn't be discouraged, but I can't

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1 rationalize it, so I guess I will agree with the  
2 Committee.

3 Is that clear for seven, now?

4 DR. LIPICKY: Yes.

5 CHAIRMAN PACKER: We are saying -- we are  
6 not saying drive carefully, we are saying don't drive.

7 DR. LIPICKY: Yes. No, you are being very  
8 explicit about how to drive carefully. Marvin has a  
9 problem.

10 DR. KARKOWSKY: How do you know this isn't  
11 the same thing for inotropes? I mean, the mechanisms  
12 may not --

13 DR. LIPICKY: He is worried about  
14 hypotension, and Milrinone was included in one of the  
15 exclusions because it is known to also dilate.

16 CHAIRMAN PACKER: I guess we are saying we  
17 don't drive when it is raining, or something. I don't  
18 know.

19 DR. LIPICKY: Right. I'm not sure which,  
20 but be more explicit.

21 CHAIRMAN PACKER: What are the non-mortal  
22 adverse effect --

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1 DR. LIPICKY: There is another complaint.

2 CHAIRMAN PACKER: What is that?

3 DR. LIPICKY: Another complaint.

4 DR. HORTON: Darlene Horton from Scios.

5 Just a point of clarification. Were you only  
6 referring to IV vasodilators and Milrinone, or were  
7 you lumping Dobutamine into that statement?

8 We did not share with you that there are  
9 44 patients who had gotten Dobutamine and Natrecor,  
10 this is in 325 and 326. And the safety profile  
11 reflects those patients in the greater data base. But  
12 there are fewer patients that received concomitant IV  
13 vasodilator therapy along with Natrecor.

14 DR. PIÑA: Yes, but they weren't on  
15 Dobutamine when you started the Natrecor drip. They  
16 couldn't have been on Dobutamine.

17 DR. HORTON: That is correct, I'm sorry,  
18 that is correct. They had Dobutamine added to  
19 Natrecor.

20 DR. PIÑA: They were clean until they  
21 started the Natrecor drip, and then someone added the  
22 Dobutamine, later on --

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1 DR. LIPICKY: And you can start with the  
2 ED10 with Dobutamine.

3 DR. KONSTAM: I would not include  
4 Dobutamine in that list.

5 DR. LINDENFELD: Neither would I.

6 CHAIRMAN PACKER: We not only live in the  
7 ED90 universe, it may or may not be empiric universe.

8 I think there is a -- without belaboring  
9 this issue, because we could for quite some time, I  
10 think many of us would say that Dobutamine may or may  
11 not be a special case here, not because there is  
12 experience with it, but because its mechanism may not  
13 be potentiating of the vasodilator effects of the  
14 drug, which is the effect we are concerned about with  
15 respect to hypotension.

16 And I think that is the only guidance we  
17 can provide.

18 Eight, what are the non-mortal adverse  
19 effects of the drug; which, if any, are dose limiting;  
20 over what dose range are the effects seen, how do they  
21 compare to conventional therapy.

22 Marv?

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1 DR. KONSTAM: You know, the only ones that  
2 I will bring out are hypotension, bradycardia, and  
3 renal dysfunction. And I think these are the ones  
4 that are concerning, to me, and over what dosing  
5 range?

6 I think they are seen over the dosing  
7 range that we've been looking at, the hypotension  
8 clearly appears to be dose related. And the others I  
9 can't quite tell.

10 And how does it compare to conventional  
11 therapy? I don't know how it compares to conventional  
12 therapy. I think that it is -- I'm struck by the fact  
13 that, for example -- I think I will just bring out, at  
14 this point, that I think the appropriate comparator,  
15 in my mind, of this agent is a pure vasodilator, and  
16 probably nitroprusside.

17 And so we actually don't have that. I  
18 mean, I think that the sponsor chose to go in the  
19 direction of comparison to conventional or standard  
20 care.

21 And I understand the rationale for doing  
22 that, but we are left without a comparator to the

1 agent to which it really should be compared. Because  
2 if you really want to know the answer to these  
3 questions you have to give it to comparing to a drug  
4 of comparable beneficial profile.

5 The one piece of data that I'm struck by,  
6 in this regard, if I remember it right, is in the  
7 small group of patients in 326 that was in the  
8 standard care group that received nitroglycerin, the  
9 incidence of hypotension -- of symptomatic hypotension  
10 I believe was non existent in that group,  
11 interestingly.

12 So, you know, looking at that, I mean I  
13 guess it seems to me that based on what we see here it  
14 may be -- the hypotensive problem may be considerably  
15 more.

16 And I think with regard to the other  
17 things I think that the bradycardia and the renal  
18 dysfunction are something special about this drug,  
19 relative to other hemodynamic agents.

20 CHAIRMAN PACKER: Well, I think  
21 nitroglycerin has a bradycardiac effect when people  
22 become hypotensive, which is thought to be reflex

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1 mediated.

2 The sponsor actually refers to that effect  
3 being potentially -- it has been reported with  
4 nitroglycerin. Now, what is a little bit different  
5 about this drug, and someone help me out here, is that  
6 I think that the bradycardia with nitroglycerin is  
7 entirely related to patients who have hypotension.

8 And what wasn't exactly clear here was  
9 whether this is related to hypotension, or whether it  
10 was an additional effect of the drug. But there is a  
11 bradycardiac effect from nitroglycerin induced  
12 hypotension.

13 DR. COHN: It is kind of a vaso-vagal kind  
14 of response, visol-gerish, I guess.

15 DR. KONSTAM: I don't have any sense from  
16 the data set that that is what is going on here, with  
17 regard to the bradycardiac effect of this agent.

18 I'm not aware that the bradycardia had  
19 anything to do with the hypotensive patients. Was it  
20 -- these were separate adverse sets of adverse events,  
21 weren't they?

22 DR. HORTON: Yes, I think I can clarify a

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1 little bit better. There were seven cases of  
2 bradycardia in the .015 group within the first 24  
3 hours. But most of those cases lasted from one minute  
4 to fifteen minutes, they were self-limited. The heart  
5 rates were in the 50 range, somewhere down to 42, I  
6 believe, was the lowest heart rate.

7 One of those cases, two of those cases  
8 were associated with hypotension in the .015 group.  
9 In the .03 group there were nine cases, seven of which  
10 were associated with hypotension.

11 So in totality, with both doses, with the  
12 dose related effect on blood pressure with the higher  
13 dose you tend to get more bradycardia reported.

14 Now, I'm going to go out on a limb here  
15 and say that I think the reason why that is, is that  
16 when you are seeing gradual drops in blood pressure,  
17 say down to the 80 millimeter mercury range, and you  
18 are seeing the patient continuing to have a heart rate  
19 in the 50s, that gets reported as bradycardia.

20 Not necessarily because it is a dramatic  
21 bradycardia, I pointed out that most of these are  
22 sinus bradycardia, but it is just that physicians are

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1 concerned that there is not a corresponding increase  
2 in heart rate, so it gets reported as a bradycardia.

3 CHAIRMAN PACKER: But your answer actually  
4 reinforces Marv's concerns that the bradycardia is  
5 independent.

6 See, the impression that we have is that  
7 the nitroglycerin bradycardia is hypotension related.  
8 The way that you've just responded to his question  
9 would suggest that the bradycardia is an independent  
10 effect here, which is not blood pressure mediated.

11 DR. RODEN: She said most of it is with  
12 hypotension.

13 CHAIRMAN PACKER: No, she said that people  
14 tend to report the brady --

15 DR. KONSTAM: We have to be careful  
16 because bradycardia can also cause hypotension. So  
17 I'm not -- and maybe I'm not sure what is going on  
18 here.

19 My sense of this is, you know, the point  
20 that you are making about the nitroglycerin is pretty  
21 unusual event, I would think. This isn't something  
22 that you see every time somebody gets hypotensive with

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1 nitroglycerin.

2           And my sense of this, and if somebody  
3 wants to say, and particularly the clinicians over  
4 there, if they want to say we are wrong about this,  
5 we've got this wrong, is that the bradycardiac events  
6 that we are seeing are not some reflex response to the  
7 hypotension.

8           DR. GROSSBAR: We have argued that there  
9 is something about this product that, in a sense, does  
10 not produce as much of an increase in heart rate  
11 during the favorable hemodynamic response as others,  
12 and presented that in a favorable light, which is to  
13 say that it doesn't increase the rate pressure product  
14 and oxygen consumption.

15           I think we recognize that that isn't  
16 miraculous in some way, but it may be accompanied by  
17 some process, and we don't want to speculate on  
18 mechanisms, because we really don't know.

19           WE did a dog electrophysiologic study, it  
20 didn't reveal anything remarkable. We don't want to  
21 speculate on the mechanism, but the same mechanism  
22 that presumably preserves this heart rate from a

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1 compensatory tachycardia may, in fact, lead to some of  
2 the observations you described.

3 DR. RODEN: I think it is important to,  
4 dealing with 8C here again, is to point out that there  
5 is really no way to compare this drug with  
6 conventional therapy like nitrates or nitroprusside.

7 Of course you don't see hypotension with  
8 those drugs because you titrate and back off, and you  
9 get an immediate return of blood pressure the moment  
10 you stop the infusion.

11 So you are using them in an entirely  
12 different way. Here you have a fixed dose which  
13 simplifies the regimen considerably, because you don't  
14 have to titrate, you just start that dose.

15 It may be that if one started  
16 nitroglycerin in ED50 dose, or ED90 dose, that you  
17 might actually see some of that bradycardia, but we  
18 don't give it that way.

19 So there is really going to be no way to  
20 make a direct comparison between conventional therapy  
21 and this therapy in terms of adverse effects such as  
22 hypotension.

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1 CHAIRMAN PACKER: Okay. I think we've  
2 summarized it well. Does anyone have anything else to  
3 add?

4 (No response.)

5 CHAIRMAN PACKER: Nine. No deaths were  
6 observed during the double blind treatment period of  
7 Trials 311, 325, 326. During these trials respective  
8 following periods, there were 26 deaths, and there  
9 were a total of 34 deaths in the entire clinical data  
10 base.

11 How does drug affect mortality in acutely  
12 decompensated congestive heart failure? Marv?

13 DR. KONSTAM: We don't see any effect on  
14 mortality.

15 CHAIRMAN PACKER: Let me try -- are you  
16 saying that there is no effect on mortality, or one  
17 does not know what the effect on mortality is?

18 DR. KONSTAM: We don't see any effect on  
19 mortality. You know, I mean, I don't see anything in  
20 the data set to give me a hint that there is any  
21 effect on mortality one way or the other.

22 CHAIRMAN PACKER: Let me see if I

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1 understand this. There are two possible answers here.  
2 There is either no effect on mortality, or there are,  
3 you can't say anything about the effect of the drug on  
4 mortality. That is one and two.

5 Which do you think it is?

6 DR. KONSTAM: I mean, we don't want to get  
7 into a discussion about equivalence trials, and  
8 whether this --

9 CHAIRMAN PACKER: No, no, we don't want to  
10 do that. I just want to know what your feelings are,  
11 one or two? One, that there is no effect of the drug  
12 on mortality; two we do not know what the effect of  
13 the drug on mortality is.

14 DR. KONSTAM: Big difference.

15 DR. MOYE: I'm going to try to rise to  
16 Marv's defense here. It is clear that this clinical  
17 program, this research program was not designed to  
18 look for mortality effect.

19 It doesn't have the resolving power it  
20 needs to be able to identify mortality effect. Having  
21 said that, we are not in a situation where all of the  
22 deaths occurred in one group or the other group.

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1       There  
2       are no deaths.

3                   CHAIRMAN PACKER:  There are 34.  No, that  
4       is after the follow-up period.  I mean, you can look  
5       at the follow-up period, that would be fine.

6                   DR. MOYE:  I'm talking about the entire  
7       program.

8                   DR. KONSTAM:  How about if I answer the  
9       question this way.  There is no effect on mortality to  
10      the level that raises my concern with regard to this  
11      agent.

12                   CHAIRMAN PACKER:  When you have no data  
13      how can you say anything about anything?

14                   DR. COHN:  -- unreasonable in their  
15      judgement, and this drug given for 24 hours, there is  
16      no reason why one would anticipate --

17                   CHAIRMAN PACKER:  Just suppose this drug  
18      were IV Milrinone, and I -- or PO Milrinone, or you  
19      know, PO - give me the most toxic drug you can think  
20      of.  Flecainide.  Any drug you want.

21                   DR. RODEN:  Let me tell you that in caps  
22      there was zero mortality signal when flecainide was

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1 compared to placebo, none, zero, they were exactly the  
2 same number of deaths. So I think that the answer is  
3 that you have no data.

4 DR. KONSTAM: Well, that is what I've been  
5 saying.

6 CHAIRMAN PACKER: No. There is a  
7 difference between saying there is no effect on  
8 mortality than saying that you do not know what the  
9 effect of mortality --

10 DR. KONSTAM: We know the effect on  
11 mortality up to some certain limit that somebody would  
12 have to calculate in order to know. I don't know what  
13 that limit is.

14 DR. LIPICKY: Have you done that? Do you  
15 know what the upper 95 percent confidence limit would  
16 be on the odds ratio?

17 DR. GROSSBAR: Yes, versus placebo the 95  
18 percent for an increase in mortality versus placebo  
19 is, I think, 1.8 percent.

20 DR. LIPICKY: 1.8.

21 DR. GROSSBAR: Greater than placebo, 95  
22 percent.

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1 DR. LIPICKY: Right.

2 DR. GROSSBAR: And I think versus active  
3 control it is about 3.6 percent, or something like  
4 that. 3.8 percent.

5 CHAIRMAN PACKER: We can make this very,  
6 very clear, and try to put this into proper  
7 perspective. If the division wanted to put something  
8 in the labeling about mortality, would the wording be,  
9 this drug has no adverse, or this drug has no effect  
10 on mortality, or would the labeling be the effect of  
11 this drug on mortality is unknown?

12 DR. KONSTAM: I don't think --

13 DR. LIPICKY: I would have a third  
14 alternative, that there could be wording that says  
15 that there are insufficient numbers of deaths in the  
16 studies to have a good estimate that --

17 CHAIRMAN PACKER: It is the same as saying  
18 that the effect on mortality is unknown.

19 DR. LIPICKY: That the upper 95 percent  
20 confidence limit odds ratio was 1.8 for placebo, so it  
21 could be as great as --

22 CHAIRMAN PACKER: Okay. So there are

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1 three possibilities.

2 DR. LIPICKY: Or it could be as low as --

3 CHAIRMAN PACKER: Right. The three  
4 possibilities are: One, saying that there is no  
5 adverse effect, or favorable effect on mortality; Two,  
6 that the number of deaths was very, very small, and  
7 the confidence intervals range from whatever it is to  
8 whatever it is. And third, the effect on mortality is  
9 unknown.

10 That is it, there are three possibilities.  
11 Let's vote. We'll just reiterate what they are so it  
12 is clear.

13 One is there is no adverse -- no favorable  
14 or adverse effect on mortality. Two, there are very  
15 few deaths, here is the point estimate in the  
16 confidence intervals. Third, we do not know anything  
17 about the effect on mortality.

18 Joann?

19 DR. LINDENFELD: I would go for the third.  
20 The effect on mortality is unknown.

21 CHAIRMAN PACKER: Lem?

22 DR. MOYE: 2.

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1 DR. PIÑA: 2.

2 DR. RODEN: 3.

3 DR. GRABOYS: 3.

4 CHAIRMAN PACKER: 3. Okay. Ten, when  
5 administered for the treatment of acutely  
6 decompensated heart failure how does the drug and  
7 conventional therapy, respectively, affect patients  
8 overall hospital stay, stability after discharge from  
9 the hospital, worsening of heart failure, incidence of  
10 re-hospitalization for congestive heart failure.

11 Marv, this probably shouldn't take that  
12 long.

13 DR. KONSTAM: I don't think there is any  
14 observed effect on any of these things.

15 CHAIRMAN PACKER: Does anyone disagree?

16 (No response.)

17 CHAIRMAN PACKER: Eleven, this is a  
18 peptide metabolized by intracellular proteolysis and  
19 by cleavage, by neutral endopeptidase. Have there  
20 been sufficient studies of pharmacokinetic drug  
21 interaction to reassure you that important drug  
22 interactions are unlikely to emerge with broader

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1 exposure.

2 We will go to Marv and then Dan on this.

3 Sorry, Dan. Marv?

4 DR. KONSTAM: Let's see, have there been  
5 sufficient studies to reassure me?

6 CHAIRMAN PACKER: Yes.

7 DR. KONSTAM: No, there have not been.

8 CHAIRMAN PACKER: Dan?

9 DR. RODEN: I'm not even sure what an  
10 inhibitor of a neutral endopeptidase would look like.  
11 I'm sure there are such things, and it is up to the  
12 Army pharmacokineticist to tell me whether those  
13 studies have been done, I guess.

14 DR. LIPICKY: They haven't been.

15 DR. RODEN: They haven't been or such  
16 things don't exist?

17 DR. LIPICKY: There haven't been, but we  
18 don't -- I guess I should also add we wouldn't know  
19 what to do.

20 DR. RODEN: So there is just no data.

21 DR. LIPICKY: But we were looking to you.

22 DR. RODEN: Well, it is like looking in a

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1 mirror, isn't it?

2 CHAIRMAN PACKER: 12. Should Nesiritide  
3 be approved for the short term, less than 24 hours  
4 intravenous in-hospital treatment of acutely  
5 decompensated chronic congestive heart failure.

6 And let me just emphasize the operative  
7 words here. Short term, less than 24 hours, in-  
8 hospital, acutely decompensated chronic heart failure.  
9 I guess that makes the issue about acute MI, takes  
10 into consideration the lack of data of acute MI.

11 And why don't we vote on that before we go  
12 to the if-sos. Marv?

13 DR. KONSTAM: I'm going to vote no, and I  
14 find it a very difficult decision, but let me just go  
15 a little bit into my reasoning.

16 You know, I guess the standard for  
17 approval is efficacy and safety, and I'm confident  
18 about the efficacy of this drug. There are safety  
19 issues, and I guess in the end it becomes a judgement  
20 call about whether the safety issues are sufficient to  
21 prevent approvability. And then there are also usage  
22 issues.

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1           And I think there are concerns about both  
2 of those. Let me just first say, in general terms, I  
3 guess I then, you know, trying to get that cost  
4 benefit analysis into my own personal judgement, I am  
5 influenced by the relative role of particular agent  
6 compared to other agents that are available.

7           And I don't see any evidence here that  
8 this agent is better than available intravenous  
9 vasodilator agents. I don't see that anywhere in the  
10 data set.

11           Nor do I have a strong suspicion that that  
12 is the case, based on the data set.

13           And so given that I guess I tend to be  
14 very sensitive to the concerns that I have, and I have  
15 a number of them. I think the adverse effects that  
16 we've talked about continue to be concerning.  
17 Hypotension is not concerning in and of itself, in a  
18 vasodilator, but this is clearly not an ideal  
19 situation in terms of the rapid offset of the  
20 potential hypotensive effects.

21           The renal dysfunction is confusing to me.  
22 I think there is some level of renal dysfunction, I'm

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1 not sure why it is occurring, I'm not sure in whom it  
2 is occurring, I'm not sure precisely what the long  
3 term consequences of it might be. Maybe it is okay,  
4 but the data set is too small to really reassure me of  
5 that.

6 The bradycardia is there. Again, I don't  
7 quite understand it. The fact that I don't understand  
8 some of these adverse effects just raises my anxiety  
9 level about them.

10 And then there are a number of unknowns.  
11 We talked about the dose response. I probably could  
12 get myself to a level of acceptance of what we know  
13 about the dose response, but it is a little bit of a  
14 question mark.

15 Again, there are no comparative data with  
16 other vasodilator agents, precisely, and we talked  
17 about the fact that there are not -- there is  
18 virtually no data about concomitant use of other  
19 intravenous vasodilator agents.

20 We can say that it would be  
21 contraindicated, but the usage out there will seep in,  
22 and we don't have any information about that, at all.

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1 And let me just add one final point, which really  
2 hasn't been brought up until now.

3 You know, when I use intravenous inode  
4 dilators, let's call them for lack of another word, in  
5 a setting of acutely decompensated heart failure,  
6 frankly one of the reasons I'm doing that is to  
7 facilitate diuresis and retain renal function.

8 And that is really, and it has been said  
9 that usually these patients are on diuretics because  
10 you are trying to diurese them, and so it is not yes,  
11 lower wedge pressure, but we really haven't talked  
12 about the fact that one of the key reasons for using  
13 these agents is to facilitate diuresis while  
14 protecting renal function.

15 And I, based on what I see here, I would  
16 not use this drug compared to the other drugs that I  
17 have.

18 So for all those reasons, at this point,  
19 I would vote no.

20 CHAIRMAN PACKER: Ray?

21 DR. LIPICKY: Can I argue with you for  
22 just a moment? The basis of approval usually is that

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1 the drug in question is better than nothing at all.  
2 And there is rarely a requirement that to approve a  
3 drug it needs to be better than something other than  
4 placebo.

5 With the exception being that when there  
6 is some adverse effect, that may be very worrisome,  
7 one might then say the other drugs that are available  
8 for treatment don't have that adverse effect, and  
9 consequently would only make sense to use the new one  
10 if, in fact, it had an advantage over any of the ones  
11 that were there.

12 And then one would want a head to head  
13 comparison that actually may have some demonstrated  
14 advantage. It isn't clear to me that what you said  
15 puts this in the category where there is some adverse  
16 fact that would put this in that category, and then  
17 you are just kind of making a value judgement about  
18 what else is there, and that shouldn't be part of your  
19 thinking process, I don't think.

20 DR. KONSTAM: Right. My sense is that my  
21 opinion without the data is that it probably isn't in  
22 that category. And I can go through why.

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1 DR. LIPICKY: Well, that is okay, but you  
2 don't have the data. And you should only be making  
3 your decision on the basis of whether or not this is  
4 better than nothing.

5 DR. KONSTAM: Well, I mean, I followed  
6 your logic up until that point. I mean, I'm with you  
7 in terms of, you know, I understand the criteria for  
8 approvability, and so that is why I went through it.

9 I mean, I think that there are safety  
10 concerns here. We don't have the data that I would  
11 like to see, specifically, which is a head to head  
12 comparison between this agent and nitroprusside.

13 DR. LIPICKY: And what would you require  
14 for that?

15 DR. KONSTAM: I'm sorry?

16 DR. LIPICKY: Let's say you were designing  
17 a trial that was head to head, Nesiritide versus  
18 nitroprusside.

19 DR. KONSTAM: Right.

20 DR. LIPICKY: On what basis would you make  
21 the decision that now it was approvable?

22 DR. KONSTAM: I would design a trial that

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1 would achieve comparable efficacy of two -- of the two  
2 vasodilating agents.

3 DR. LIPICKY: How would you -- for wedge  
4 pressure?

5 DR. KONSTAM: I would go for wedge  
6 pressure with effects confirmed by symptomatology.

7 DR. LIPICKY: And you think that you would  
8 be able to design the equivalence of a non-equivalence  
9 trial using wedge pressure as an endpoint?

10 DR. KONSTAM: Well, the purpose of the --

11 DR. LIPICKY: How would you get -- so  
12 let's say the two drugs were within one millimeter of  
13 mercury wedge pressure, millimeter, is that good  
14 enough?

15 DR. KONSTAM: Yes.

16 DR. LIPICKY: Well, you would never get  
17 that, right? How would you get that?

18 DR. KONSTAM: I'm not concerned about this  
19 drug beating nitroprusside in efficacy.

20 DR. LIPICKY: But how would you know they  
21 are equivalent in efficacy; what measure would you  
22 use?

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1 DR. KONSTAM: Okay, well I just said it.  
2 You want me to specify within what range of wedge  
3 pressure?

4 DR. LIPICKY: Well, clearly, because okay,  
5 how would you know you had equivalent efficacy, would  
6 one millimeter mercury wedge pressure, when, at what  
7 time?

8 DR. KONSTAM: Well, we could work those  
9 questions out. I don't know whether you want me to  
10 commit myself on that right now.

11 DR. LIPICKY: Well, but you really think  
12 you could?

13 DR. KONSTAM: Yes, it has been done  
14 before, and it has been in other -- there have been  
15 other comparative hemodynamic studies where agents  
16 effects on hemodynamics were matched, and they have  
17 been done fairly successfully.

18 I don't know whether -- I don't know how  
19 to answer the question in terms of within how many  
20 millimeters of mercury wedge pressure, of the top of  
21 my head.

22 DR. LIPICKY: Did the successful trials

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1 did that? I mean, they had some specification for  
2 millimeters of mercury at some point in time?

3 DR. KONSTAM: Probably.

4 DR. LIPICKY: Of the 24 hour day? I doubt  
5 it. You eyeball the data and say it looks the same.

6 DR. KONSTAM: I'm not sure what you are  
7 asking, Ray.

8 DR. LIPICKY: Well, I don't think you can  
9 get a trial like you want.

10 DR. KONSTAM: I do.

11 DR. LIPICKY: Okay.

12 DR. KONSTAM: But let me -- I mean, if you  
13 want to ask what trial I would like to see to get me  
14 to the level of approvability, that would be the trial  
15 I would design. I think we are still faced right now  
16 with approval or not.

17 And let me just say that, you know, I'm  
18 really at the point that you described, without the  
19 data. That is to say that I -- we have other  
20 vasodilator, we have nitroprusside, and without having  
21 the data in front of me, I'm going to go so far as to  
22 say that I'm concerned that this drug is less safe

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1 than nitroprusside.

2 With regard to the hypotensive effect I  
3 think it is going to be comparable, but nitroprusside  
4 is probably an easier drug to titrate than this drug.

5 And with regard to the renal  
6 insufficiency, and the bradycardia, I'm not aware that  
7 that is going to be a concern for me with  
8 nitroprusside.

9 So without the data comparatively, but  
10 with the significant, you know, history of clinical  
11 use of the agent, that is where I am.

12 CHAIRMAN PACKER: Tom, do you want to  
13 start?

14 DR. GRABOYS: I think it is really coming  
15 down to the wire, and kind of agonize back and forth  
16 on it. But I think the drug does expand our  
17 therapeutic modalities for treating this problem,  
18 which is of significant magnitude, and I would vote  
19 for approval.

20 CHAIRMAN PACKER: Dan?

21 DR. RODEN: I agree with everything that  
22 Marv says, but I'm going to vote for approval. I'm a

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1 yes.

2 CHAIRMAN PACKER: Cindy's vote is yes.

3 Joann?

4 DR. LINDENFELD: I would vote yes. I  
5 don't have -- I agree with everything Marv said but I  
6 think the drug is effective, and I think it would help  
7 us, so I vote yes.

8 CHAIRMAN PACKER: Lem?

9 DR. MOYE: I vote no. I agree with what  
10 Marv has said, and I have some serious reservations  
11 about the protocol, and the design of this study,  
12 which makes me wonder whether in fact this medication  
13 is better than placebo.

14 CHAIRMAN PACKER: Ileana?

15 DR. PIÑA: I've been back and forth in my  
16 own mind, and I think I'm coming down on Marv's side,  
17 I'm going to agree with Marv, I'm going to say no.

18 CHAIRMAN PACKER: Vote is no. What is the  
19 vote so far?

20 DR. LIPICKY: Don't tell them, Joan.

21 CHAIRMAN PACKER: Four yes and three no?

22 It doesn't matter.

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1 My own sense, I think there are a lot of  
2 deficiencies in this data base. I think that there  
3 are real concerns about the -- I'm personally  
4 concerned about the lack of acute MI data. I think  
5 the drug is going to be used in acute MI, and I think  
6 that we need that kind of data.

7 I'm concerned about a number of the  
8 confounding issues with respect to symptoms. I'm  
9 concerned, I think, about the fact that I guess of all  
10 the side effects the one that puzzles me the most is  
11 the renal issue, which I don't understand.

12 And I wish I understood better, and it  
13 might just require more patience to understand it  
14 better. And you know I must say I'm not certain I  
15 share Marv's concerns, because I really think that I  
16 would like to view this drug on its own merits, and  
17 not so much how it compares to available agents.

18 That is really going to be determined by  
19 the marketplace, and physician's use of the drug. And  
20 I just think there is a lot of other questions and  
21 issues that the sponsor could have addressed.

22 Having said that I guess I would agree

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1 with Tom that there is something that this drug may do  
2 for patients that isn't available right now. I view  
3 this as being an extremely close call, but I guess I  
4 would come down and say yes.

5 DR. LIPICKY: So then you have to  
6 continue.

7 CHAIRMAN PACKER: You have 5/4 in favor?  
8 5/3.

9 DR. LIPICKY: So you have to answer the  
10 rest of the questions.

11 CHAIRMAN PACKER: Now you have to answer  
12 the rest of the questions.

13 What dosing regimen should be specified  
14 for use -- Marvin, it is going to be hard for you to  
15 answer these questions.

16 DR. KONSTAM: Well, I didn't read past  
17 here, okay? I think this is one of the concerns.  
18 I'm not quite sure, now I see whether I'm a ED90 or a  
19 10 guy. I think the dose that is being recommended is  
20 the .015 dose.

21 I think that is reasonable. I'm not sure  
22 how to titrate it above and below that dose. I think

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1 it would be reasonable to recommend a dose half that  
2 amount, and titrate it up.

3 Again, the problem there is we don't know  
4 anything about titration in clinical practice. So  
5 that is my answer. Did I answer?

6 CHAIRMAN PACKER: 0.15.

7 DR. KONSTAM: 0.015.

8 CHAIRMAN PACKER: 0.015 I guess up to  
9 0.03? No. I'm sorry, forgive me, summarize?

10 DR. LIPICKY: Paraphrasing Marvin's  
11 statements one would put in the dosing instructions  
12 the doses that were studied and say, use your best  
13 judgement.

14 CHAIRMAN PACKER: Okay. And the clinician  
15 should do that based on whatever they do to make the  
16 decisions that they make?

17 DR. LIPICKY: However they make decisions.

18 CHAIRMAN PACKER: Does anyone disagree  
19 with that?

20 DR. RODEN: Ray, I still think you ought  
21 to have a chance to look at the PKPD data as they  
22 emerge, and see if there is any suggestion that we

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1 ought to reconsider that, and I actually would be in  
2 favor of recommending a bolus, because that is the  
3 regimen that was used.

4 CHAIRMAN PACKER: Let's move forward to  
5 12B. What level of care should be recommended?  
6 Sponsor is seeking claim for being able to infuse this  
7 without a catheter in place. How does the Committee  
8 feel about this? Marv.

9 DR. KONSTAM: Yes, my feeling about this  
10 is that there is likely to be significant risk if the  
11 drug is infused in patients with normal wedge  
12 pressures. I think that is, to me, the real issue  
13 here, the principal issue here.

14 And you know, I don't know how to come  
15 down on that. I mean, I would feel sympathetic to  
16 some commentary to that effect. And saying that, you  
17 know, if there is any question based on clinical  
18 assessment, that the wedge pressure is normal then a  
19 Swan has to go in before it is used, rather than  
20 requiring that Swans routinely be used.

21 CHAIRMAN PACKER: So your vote is to say  
22 that invasive monitoring should be carried out?

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1 DR. KONSTAM: No. What I said is that I  
2 think the drug should be used where there is a degree  
3 of clinical certainty that we are dealing with a  
4 patient with a high wedge pressure.

5 CHAIRMAN PACKER: How would one know that?

6 DR. LIPICKY: When you are in doubt, go to  
7 a Swan.

8 DR. KONSTAM: There are patients in whom  
9 you can be absolutely confident you are dealing with  
10 a high wedge pressure. And if I had that patient in  
11 front of me, and I knew it, I would feel comfortable  
12 using the drug in that situation.

13 CHAIRMAN PACKER: Okay. Dan?

14 DR. RODEN: I think given all the  
15 uncertainties about the drug, and the use of the drug,  
16 and the regimen we should use, and whether it is  
17 actually predictable that hypotension will or won't  
18 occur, and the sense that there were certainly some  
19 patients screened for the drug, for whom the  
20 pharmacist mixed up a drug, and then they were found  
21 not to have wedge pressures in the qualifying range,  
22 I would actually insist that they have a pulmonary

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1 catheter in place.

2 CHAIRMAN PACKER: We have two different  
3 recommendations. Does anyone have yet another  
4 different recommendation, so that we can take a vote?  
5 Tom?

6 DR. GRABOYS: Can it be in the package  
7 insert that the manufacturer strongly urges the use of  
8 invasive hemodynamic monitoring?

9 DR. GROSSBAR: I just want to remind the  
10 Committee, the day is long, that the vast majority of  
11 the patients you've been discussing from the safety  
12 point of view were derived from a study where there  
13 was no invasive hemodynamic monitoring.

14 You are inferring, a lot of information  
15 about symptomatic hypotension, and your worst case or  
16 your fears are based on patients who were not, in  
17 fact, monitored for their wedge pressure before they  
18 were treated.

19 So, I don't know, necessarily whether that  
20 pulls one side or the other, but I just wanted to  
21 remind you that 200 plus of the patients were from --

22 DR. KONSTAM: Can I go with that? Would

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1 you agree with me that the biggest safety concern with  
2 regard to hypotension would be in patients with normal  
3 wedge pressures in whom this is given to?

4 DR. GROSSBAR: I'm not a cardiologist, and  
5 I'm not sufficiently expert to make that judgement.  
6 But I would say that I think that the same tools that  
7 people use, to use these other drugs which have been,  
8 I think, cavalierly described as we know how to use  
9 it, we just do this, and everything works out, is not  
10 really necessarily of what actually happens.

11 When I've read papers on nitroprusside for  
12 the treatment of post-operative hypotension, there is  
13 a lot of hypotension reported there. So maybe you can  
14 get rid of it fast, I can't quarrel with that, but it  
15 happens.

16 So I think we don't know anything more  
17 than what we've tested. I'm sure even if we said we  
18 did, Dr. Lipicky wouldn't let us say it anyway, so it  
19 doesn't really matter if we speculate on it.

20 CHAIRMAN PACKER: Okay. Let's take a  
21 vote. The vote is I guess three choices. One, there  
22 should be no -- the general way that it is done right

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1 now is, or I shouldn't say the general way it is done  
2 right now.

3 One way which is commonly -- that commonly  
4 appears in labeling is it should be infused under  
5 close supervision. I think the sponsor actually is  
6 proposing something like that, so that is choice  
7 number one.

8 Choice number 2 is Marv's recommendation,  
9 which is close supervision plus the clinical assurance  
10 or belief, or whatever the word is, that feeling  
11 pressures are elevated.

12 And the third is invasive monitoring.

13 Marv, do you want to lead us off? Or is  
14 that two? Joan, we will go around this way.

15 DR. LINDENFELD: I like Marv's statement,  
16 I think two. I'll go with Marv, 2.

17 CHAIRMAN PACKER: 2. Lem?

18 DR. MOYE: I think Marv is right again.  
19 2.

20 DR. PIÑA: 2.

21 DR. GRABOYS: 3.

22 DR. RODEN: 2.

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1                   CHAIRMAN PACKER: I will vote 3. Only  
2 because the fact that, you know, I think we need to  
3 know more about the drug, and until we know more about  
4 the drug I would like to see the patients be as  
5 carefully monitored as possible. That is the only  
6 reason I vote 3.

7                   But what was the vote? There were two 3s,  
8 and the rest were 2s. And Cindy I think votes  
9 essentially -- well Cindy did not have the option of  
10 Marv's choice, so she did not favor invasive  
11 monitoring, so I think that would be the only thing we  
12 could say from what she has said.

13                  DR. LIPICKY: I need to ask one question  
14 that you guys know the answer to. Somewhere didn't  
15 we, in the back of my mind, I remember there was a  
16 trial that said that people with heart failure who had  
17 Swan-Ganz in and who did not, were able to be  
18 differentiated.

19                  CHAIRMAN PACKER: It wasn't a trial, it  
20 was a case control study with a relative risk of 1.24.

21                  DR. LIPICKY: Thank you, okay.

22                  CHAIRMAN PACKER: We've already had a

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1 Committee meeting in the past as to whether in a case  
2 control study with a relatus of 1.24 means. It wasn't  
3 last night, no.

4 CHAIRMAN PACKER: 12C, what warnings or  
5 precautions should be emphasized in the package  
6 insert?

7 DR. LIPICKY: I have that from you guys  
8 already.

9 CHAIRMAN PACKER: Terrific. Can I make a  
10 recommendation that we skip 13. There are two reasons  
11 for making that recommendation. One is the lateness  
12 of the hour, so I'm not exactly certain when we will  
13 have the vigorous discussion this question deserves.

14 More importantly I'm not exactly certain  
15 that the global issues that are reflected in 13 are  
16 most appropriately discussed in the context of this  
17 NDA.

18 DR. LIPICKY: Right.

19 CHAIRMAN PACKER: So we will take a rain  
20 date on question 13.

21 DR. LIPICKY: But on your way home, or at  
22 least tonight I would like you to lose a little bit of

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1 sleep, as you contemplate why you were willing to take  
2 action, bunches of actions on side effects, right?  
3 And you even concluded that hypotension was dose  
4 related.

5 You never asked the question was this an  
6 intent to treat analysis, you never asked the question  
7 was this a pre-specified endpoint? You never came to  
8 any kind of -- you never agonized over whether you  
9 could believe the data because it must have fit your  
10 model.

11 I just want you to lose sleep.

12 DR. MOYE: We agonized about those from  
13 the inception of the conversation today, even about  
14 the main discussions.

15 CHAIRMAN PACKER: We will take Ray's  
16 advice and guidance, and the meeting is adjourned.

17 (Whereupon, at 4:00 p.m. the above-  
18 entitled matter was concluded.)

19

20

21

22

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**CERTIFICATE**

This is to certify that the foregoing transcript in the  
matter of:                   87<sup>TH</sup> 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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UNIQUE WORDS: 3,143
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