

UNITED STATES OF AMERICA  
 DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 FOOD AND DRUG ADMINISTRATION  
 CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

+ + + + +

92nd MEETING

+ + + + +

FRIDAY,

MAY 25, 2001

+ + + + +

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

PRESENT:

MILTON PACKER, M.D., Chairman

MICHAEL F. ARTMAN, M.D., Member

JEFFREY BORER, M.D., Member

RALPH D'AGOSTINO, Ph.D., Temporary Voting Member

THOMAS GRABOYS, M.D., Member

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## PRESENT (Continued):

ALAN T. HIRSCH, M.D., Member

MARVIN KONSTAM, M.D., Temporary Voting Member

JOANN M. LINDENFELD, Member

STEVEN NISSEN, M.D., F.A.C.E., Member

ILEANA PINA, M.D., Member

JOAN C. STANDAERT, Executive Secretary

C-O-N-T-E-N-T-S

PAGE

Conflict of Interest Statement . . . . . 4

Natrecor NDA 20-920 (nesiritide)

Sponsor Presentation:

Introduction, Michael Crockett . . . . . 5

Original NDA 20-920, Raymond Lipicky, M.D. 11

NDA Amendment Trial Designs, Darlene P. Horton, M.D. . . . . 23

VMAC Amendment Trial Designs, James B. Young, M.D. . . . . 100

Natrecor Safety, Darlene P. Horton, M.D. 177

Beneficial Assessment, William T. Abraham, M.D. . . . . 266

Committee Discussion of Questions . . . . . 279

## P-R-O-C-E-E-D-I-N-G-S

(9:02 a.m.)

CHAIRMAN PACKER: I'd like to call to order the 92nd meeting of the Cardiovascular and Renal Drugs Advisory Committee.

The Committee members are before you. We have two invited guests, Dr. Ralph D'Agostino from Boston University, and Dr. Marvin Konstam from New England Medical Center.

Joan Standaert will cover the administrative matters for this morning.

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

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

In the event that the discussions involved any other products or firms not already on the agenda for which an FDA participant has a financial interest,

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1 the participants are aware of the need to exclude  
2 themselves from such involvement, and their exclusion  
3 will be noted for the record.

4 With respect to all other participants, we  
5 ask in the interest of fairness that they address any  
6 current or previous financial involvement with any  
7 firm whose products they may wish to comment upon.

8 That concludes the conflict of interest  
9 statement for May the 25th.

10 CHAIRMAN PACKER: Thank you very much,  
11 Joan.

12 The topic for this morning is NDA 20-920,  
13 nesiritide. The proposed indication is for the  
14 treatment of acute heart failure. The sponsor is  
15 Scios, and I'll ask Dr. Crockett to begin his  
16 presentation.

17 DR. CROCKETT: Chairman Packer, Dr.  
18 Lipicky, Dr. Temple, and members of the Advisory  
19 Committee, good morning.

20 My name is Michael Crockett, and I'm the  
21 Associate Director of Regulatory Affairs at Scios.

22 Scios presented the data on the Natreacor  
23 new drug application to the Cardio-renal Advisory  
24 Committee in January of 1999. In subsequent  
25 discussions with the FDA during the summer of 1999,

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1 we and the FDA were able to develop a plan for the  
2 acquisition of additional clinical data for Natrecor  
3 that would address the remaining issues FDA had  
4 regarding Natrecor's approval for the use in acute  
5 congestive heart failure.

6 Today's presentation will focus on  
7 additional data acquired since the FDA's April 1999  
8 action letter for Natrecor and how these data do,  
9 indeed, address the FDA's remaining issues for the  
10 approval of Natrecor.

11 The agenda for today will include my brief  
12 introduction. Then Dr. Raymond Lipicky, the FDA's  
13 Director of the Cardio-Renal Drug Products Division  
14 will present an overview of the Natrecor original NDA  
15 data submitted to the agency.

16 Dr. Darlene Horton, Vice President,  
17 Medical Affairs at Scios, will focus primarily on the  
18 rationale for the VMAC trial design. VMAC stands for  
19 the vasodilation in the management of acute congestive  
20 heart failure. VMAC was Scios' primary response to  
21 the agency's request for additional data to support  
22 Natrecor's approval.

23 Dr. James Young, Section Head of the Heart  
24 Failure and Cardiac Transplant Medicine and Medical  
25 Director of the Kaufman Center for Heart Failure at

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1. the Cleveland Clinic Foundation, will then present the  
2. efficacy data on Natreacor from the VMAC trial.

3. Dr. Horton will then present the Natreacor  
4. safety profile, including the safety data from the  
5. VMAC trial. Dr. Horton will also present a brief  
6. overview of the PRECEDENT trial. The PRECEDENT trial  
7. was a double blinded comparison of Natreacor to  
8. dobutamine. PRECEDENT stands for the prospective  
9. randomized evaluation of cardiac ectopy with  
10. dobutamine or Natreacor therapy.

11. And a benefit-risk assessment will be  
12. presented by Dr. William Abraham. Dr. Abraham is the  
13. Chairman of the Department of Cardiology at the  
14. University of Kentucky, College of Medicine.

15. My introduction will first include a brief  
16. discussion of the names and the structure of Natreacor.  
17. I will provide a brief outline of Natreacor's  
18. regulatory and clinical highlights. I will conclude  
19. with the review of the FDA's recommendations to Scios  
20. and the studies included in the NDA amendment that  
21. serve as the basis for today's presentation.

22. The scientific name for Natreacor is human  
23. B-type natriuretic peptide or hBNP. The proposed USAN  
24. name currently under consideration is "nesiritide."

25. Go ahead. I was just making sure

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1 everybody had a chance to turn around.

2 Scios utilizes the recombinant  
3 manufacturing process to produce the 32 amino acid  
4 peptide product with the trade name Natrecor. Scios  
5 has demonstrated that Natrecor is chemically and  
6 structurally identical to endogenous hBNP. Natural  
7 occurring hBNP is produced by the body's cardiac  
8 ventricles.

9 The IND for Natrecor was filed  
10 approximately eight years ago. Clinical development  
11 commenced shortly thereafter.

12 Listed here in both white and yellow are  
13 eight studies conducted in acute congestive heart  
14 failure patients that were submitted in the original  
15 NDA in April 1998. The three studies highlighted in  
16 yellow at the bottom of this slide were the pivotal  
17 studies that supported the efficacy and safety  
18 outlined in the original NDA.

19 I will remind you that Dr. Lipicky will  
20 later provide an overview of the original NDA program.

21 Shortly after the filing of the original  
22 NDA for Natrecor, the PRECEDENT trial was initiated.  
23 As mentioned, Dr. Horton will review this trial later  
24 today.

25 However, the purpose of the PRECEDENT

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1 trial was to compare the effects of fixed dose  
2 infusions of Natrecor and dobutamine on  
3 arrhythmogenesis and heart rate.

4 Nine months after filing the NDA, Scios  
5 presented Natrecor for the first time before the  
6 Advisory Committee. In its April action letter, the  
7 FDA indicated to Scios that additional data to support  
8 Natrecor's approval would be required. The FDA stated  
9 that it was "a particularly difficult decision" to not  
10 approve Natrecor.

11 Scios responded to the FDA's action  
12 letter, and in the next six months, we met with the  
13 agency about its concerns, and we agreed on the  
14 parameters of a new clinical trial to gather  
15 additional data needed for approval. That trial was  
16 the VMAC study.

17 Although the nonapproval to the original  
18 Natrecor NDA was difficult, we believe that today we  
19 have actually a stronger clinical data set supporting  
20 the safety and efficacy of Natrecor in the treatment  
21 of acute decompensated congestive heart failure.

22 The FDA issues fell basically into the  
23 following areas: the pharmacodynamic profile;  
24 expansion of efficacy and safety database,  
25 particularly in the incidence and impact of

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1 symptomatic hypotension.

2 We were to conduct a double blinded  
3 comparison to placebo and to compare Natreacor to a  
4 commonly used IV vasodilator. Please keep in mind  
5 that the placebo was actually standard therapy for  
6 these patients.

7 In addition, there was to be no exclusion  
8 of patients with an ejection fraction greater than 40  
9 percent or patients with active ischemia. IV  
10 nitroglycerine was selected as the comparator because  
11 it's a vasodilator, and nitroglycerine is frequently  
12 used in the treatment of patients with acute  
13 decompensated congestive heart failure.

14 The agency also recommended that the trial  
15 design include dose adjustments of Natreacor.

16 Another good choice as a comparator might  
17 have been IV sodium nitroprusside, but because the  
18 VMAC trial design enrolled non-catheterized patients  
19 and active ischemia patients, we concluded that  
20 including sodium nitroprusside was not appropriate as  
21 the comparator drug.

22 There was also no requirement to show that  
23 Natreacor's superiority over that of IV nitroglycerine  
24 in the VMAC trial.

25 In October 1999, six months after the

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1 FDA's action letter, the first patient was enrolled in  
2 the VMAC clinical trial. The NDA amendment for  
3 Natrecor, Scios' official response to the FDA's action  
4 letter, was submitted in January 2001. Along with the  
5 VMAC trial results, we also submitted results from the  
6 PRECEDENT trial, which as I stated earlier was ongoing  
7 at the time of the original NDA review.

8 Scios believes that Natrecor given  
9 intravenously for relatively short periods of time is  
10 safe and effective in patients with acute  
11 decompensating congestive heart failure. We look  
12 forward to presenting our data today since we believe  
13 that Natrecor can play an important role in the  
14 physician's ability to treat patients with this  
15 serious disease.

16 Including these trials, a total number of  
17 patients treated with Natrecor currently approaches  
18 1,000, and Dr. Lipicky will now explain the results  
19 from the first 500 patients.

20 Dr. Lipicky.

21 DR. LIPICKY: I suggested that I present  
22 for the company the prior results, and that it had to  
23 be presented because many on the Advisory Committee  
24 have not seen that thing.

25 But based on the first submission, five

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1 out of the three, or five of eight who were here,  
2 voted for approval, and three of eight did not, and in  
3 fact, we eventually decided that that was not a good  
4 recommendation, and so on and so forth.

5 So the original content isn't going to be  
6 reviewed today, but you deserve an overview, and the  
7 thing that I wanted to do was -- next slide -- to  
8 point out some features of what happened.

9 This slide should really start in 1987.  
10 That is the last approval date for an intravenous  
11 therapy for acute heart failure, and that approval was  
12 based entirely on pulmonary capillary wedge pressure  
13 change.

14 And so from 1987 to the present day, there  
15 have been enormous changes in what one thinks one  
16 ought to know for the approval of something that IV in  
17 hospital for acute heart failure, and it is during the  
18 midst of all of that that the nesiritide program  
19 began, and is now culminating.

20 In 1996, it's important to look at what we  
21 said was the basis for approval if their data showed  
22 it, and that was that the primary endpoint would be  
23 pulmonary capillary wedge pressure and that pulmonary  
24 capillary wedge pressure would be sufficient; that  
25 there ought to be interest in developing some feeling

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1 for do patients feel good in addition to pulmonary  
2 capillary wedge pressure, but that it was unclear  
3 where that sat in the relative hierarchy of what has  
4 to be know.; and that there would not need to be any  
5 more than 500 patients in the total database, and an  
6 NDA could be submitted.

7 So those were the kind of standards that  
8 were developed by us in 1996.

9 Next slide.

10 That advice resulted in seven trials, five  
11 placebo controlled, one placebo and active control and  
12 one active control. Now, all of those trials I'm not  
13 going to summarize, but what it amounted to was a  
14 total of 721 studied subjects, 505 treated with  
15 nesiritide. We said they needed 500, and since it was  
16 placebo controlled, there was 93 percent of those  
17 patients were Class III or IV, but only 37 percent of  
18 those patients were Class IV at the time of being  
19 randomized, and in part, that was because -- next  
20 slide -- almost all of the slides were parallel  
21 placebo controlled trials.

22 A variety of things, and this is only  
23 meant to say that they're mainly parallel trials, a  
24 lot of different dosing regimens, bolus doses, bolus  
25 plus infusion, and so on and so forth. I'm going to

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1 ignore all of that. That will be covered in the  
2 things that will be discussed with VMAC and why the  
3 dose in VMAC is the right dose.

4 Next slide.

5 And the only thing I want to point out is  
6 that compared to placebo, there isn't any question  
7 that pulmonary capillary wedge pressure is changed,  
8 and if you pay attention to this trial, which was only  
9 40 patients big, but where the dose of the nesiritide  
10 was varied by a function of threefold in each dosing  
11 arm, the very clear dose response that you see, and in  
12 general, the lowest bar, the closest bar to placebo is  
13 the lowest dose studied, and in general there is a  
14 dose response relationship that's seen almost always,  
15 but the difference in doses here are very small,  
16 sometimes only a factor of two.

17 So there's clearly a change in pulmonary  
18 capillary wedge pressure, and it is a function of  
19 dose. This is the retrospective meta analysis that  
20 has a nominal p value of .0001.

21 Next slide, please.

22 And cardiac index similarly goes in the  
23 right direction, and very little doubt that, in fact,  
24 it changes properly by this meta analysis. No one had  
25 trouble with this. It was pretty much true in every

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1 study looked at, and so on and so forth.

2 Next slide.

3 The hemodynamic effect that was observed  
4 in general developed, took a while to get to its peak,  
5 and was relatively sustained over the duration of a  
6 24-hour infusion.

7 Next slide.

8 Now, one trial, Trial .325, attempted to  
9 evaluate symptoms so that patients when they were  
10 randomized were asked at the end of six hours to  
11 determine whether they were as short of breath as they  
12 were just before they were randomized. So this is a  
13 patient evaluation of dyspnea.

14 And, indeed, all of the patients in the  
15 trial were catheterized and had evaluations of  
16 hemodynamics that were going on concurrently.

17 Six hours is the time when placebo  
18 stopped. So this is a six hour placebo controlled  
19 trial, and for four to six hours prior to  
20 randomization, IV diuretics were withheld. So there  
21 was no recent, I guess no real recent therapy given,  
22 and you can see the results, highly statistically  
23 significant.

24 Next slide, please.

25 And the relationship between worsening, no

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1 change, and improved for change in pulmonary wedge  
2 pressure was reasonably correlated, that is, if the  
3 pulmonary capillary wedge pressure went up and people  
4 got worse; if the pulmonary capillary wedge pressure  
5 went down, people got better. And that was the kind  
6 of correlation, but not much can be said about that.

7 Next.

8 And parallel to this, there was another  
9 global assessment of clinical status that was made by  
10 subjects themselves responding to questions sometimes  
11 asked by the investigator, but often by nurses or  
12 study coordinators and the physician global status.

13 And, again, there's a very clear  
14 difference between drug and placebo, and it sort of  
15 almost looks like it's related to dose.

16 Next slide, please.

17 And after six hours, placebo was gone and  
18 standard therapy in any therapy as given, and then  
19 pretty much things sort of evened out, but nesiritide  
20 seemed to be better by point estimate.

21 Next slide.

22 So from a pulmonary capillary wedge  
23 pressure point of view, cardiac index point of view,  
24 no question about what happened, no question about the  
25 numbers for dyspnea and global evaluation. That

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1. patients were catheterized leads to some interpretive  
2. problems with respect to whether those numbers can be  
3. interpreted religiously.

4. Then, of course, there was a dose related  
5. change in blood pressure. The nesiritide decreases  
6. blood pressure, and as you can see, it takes a while  
7. to get to its steady state, and when it is reversed,  
8. it takes a while for it to reverse.

9. And since there was active seeking of  
10. understanding of what nesiritide does, plasma  
11. concentrations of nesiritide were measured frequently  
12. during the trials, as were whether or not pulmonary  
13. capillary wedge pressure decreased, as was whether or  
14. not arterial pressure decreased.

15. And, indeed, there was a very reasonable  
16. E-max relationship between plasma concentration, hypo  
17. of blood pressure, and pulmonary capillary edge  
18. pressure, and the EC-50 were the two variables of  
19. pulmonary capillary wedge pressure and blood pressure  
20. were separated a little bit, but in essence were  
21. pretty close.

22. Now, if one looks at how accurate that  
23. data is, there's a lot of slop. You can't tell for  
24. sure whether they're different or not different, but  
25. it's close. I guess that would be the thing.

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1           So the question was: do you have to  
2 decrease blood pressure in order to get a change in  
3 pulmonary capillary wedge pressure, and at the time of  
4 the original NDA, the notion was that the doses being  
5 recommended for use based on the trials I just  
6 summarized for hemodynamic variables were sort of at  
7 the top of the dose response curve, and that  
8 hypotension wasn't well understood.

9           Next slide.

10           There wasn't much else data to look at.  
11 This was the mortality data that existed. Clearly  
12 nesiritide point estimate wasn't worse than placebo  
13 and wasn't worse than control agents.

14           There were not very many deaths at 15 or  
15 21 days, and the confidence limits were pretty wide,  
16 and one didn't know exactly what to say about that or  
17 whether that was important.

18           Next slide.

19           So we said that because of concerns that  
20 relate to the association between pulmonary capillary  
21 wedge pressure and blood pressure, because it takes a  
22 long time to come to steady state because of the  
23 pharmacokinetics and pharmacodynamics, and that  
24 because of the offset time for the same reasons, that  
25 a utility of a fixed dose regimen seemed uncertain in

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1 this clinical setting and, in particular, since it had  
2 such a long time constants; that there needed to be  
3 expansion on both efficacy and safety; and that there  
4 had to be people who were sick or more people who were  
5 sick, and that there had to be people who had an  
6 ischemic etiology for their heart failure included;  
7 and that there needed to be confirmation on the effect  
8 on symptoms.

9 And we recommended the trial that you're  
10 about to hear, and I'm through, and I won't answer  
11 questions.

12 (Laughter.)

13 CHAIRMAN PACKER: That's okay. You don't  
14 have to.

15 DR. LIPICKY: Okay.

16 CHAIRMAN PACKER: Let me just add to the  
17 background that Ray has already described to the  
18 Committee. Some of you may be wondering why this drug  
19 is coming back to the Committee when, in fact, in  
20 January of 1999 this Committee in a split vote  
21 recommended based on the data that were available at  
22 that time that the drug be approved, five to three  
23 vote.

24 I think it is always important to  
25 recognize that the vote of this Committee represents

1 a very small part of this process; that the  
2 discussions that occur during the course of any NDA  
3 actually represent more meaningful guidance to the  
4 agency than just a mere vote.

5 And during the presentation of the  
6 nesiritide NDA in January of 1999, a number of issues  
7 were raised by the Committee that subsequent to the  
8 Committee meeting were taken quite seriously by the  
9 division, and which resulted in a decision by the  
10 division to not approve the agent.

11 I had an opportunity to go back and review  
12 the notes of January 1999. I just want to highlight  
13 some of the issues that were brought forward in a  
14 matter that should complement those that Ray has put  
15 forward.

16 One, the Committee highlighted that the  
17 number of patients was relatively small, 505 treated  
18 patients, although it was the number that the agency  
19 had said to the company it needed to study.

20 Second, that there was no doubt, and the  
21 Committee agreed that this drug was hemodynamically  
22 active, and it reduced pulmonary wedge pressure, but  
23 that the Committee felt that one needed more than an  
24 effect on just wedge pressure, that one needed some  
25 sense of clinical benefit.

1           The company did evaluate symptoms and  
2 found that symptoms were improved, but there were  
3 considerable concerns raised by the Committee that  
4 knowledge of the hemodynamics had influenced the  
5 assessment of symptoms because not only had dyspnea  
6 improved, but other symptoms, unlikely to be related  
7 to wedge pressure, had improved, like appetite had  
8 improved and perhaps more strikingly, lightheadedness  
9 had improved on nesiritide compared with placebo, and  
10 consequently there was significant concerns raised by  
11 the Committee that perhaps knowing that the wedge  
12 pressure had decreased had influenced the assessment  
13 of symptoms, and since it was deemed that the  
14 assessment of the demonstration of some clinical  
15 benefit was important, otherwise wedge pressure would  
16 have been sufficient, that, in fact, one needed to  
17 have a confirmative trial on symptoms.

18           There were concerns as Ray has emphasized  
19 whether the dose was right and whether the  
20 relationship between the drop in wedge pressure and  
21 the drop in blood pressure was clinically appropriate,  
22 and concerns that to get the wedge pressure down, one  
23 had to lower the blood pressure a lot.

24           There were concerns that the NDA studied  
25 primarily stable people, patients who might not be

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1. representative of the patients who would get the drug  
2 in clinical practice, and specifically patients with  
3 an acute myocardial infarction had not been enrolled,  
4 and that was deemed to be a deficiency.

5           There were also concerns about whether the  
6 hemodynamic effects of the drug were sustained, and  
7 some question was raised about the possibility of  
8 tolerance.

9           And lastly, there were some safety  
10 concerns in addition to the hypotension. There were  
11 questions about serum creatinine that were raised at  
12 that time, and the collective, if you put all of this  
13 together and put it into one package, all of this, all  
14 of these concerns were described and discussed at  
15 length by the Advisory Committee and form the basis of  
16 a decision by the division to say we need more data.

17           And that's what bring us to this  
18 Committee. So the purpose here is to look at the new  
19 data and determine whether it addresses the concerns  
20 of the previous Advisory Committee, recognizing, of  
21 course, that this Advisory Committee is not identical  
22 to the previous Advisory Committee and may not have  
23 the same opinions as the previous Advisory Committee.

24           So I just wanted to describe how it is  
25 possible for an issue like this to come back to an

1 Advisory Committee that ostensibly had recommended  
2 approval, but it underscores the fact, I think, that  
3 the vote that we take at the end of these meetings,  
4 although it seems to generate enormous public  
5 interest, is an extremely small part of the process  
6 that we engage in, and in fact, if it were the only  
7 thing that was important, it would be the only  
8 question that would ever be asked of this Committee.  
9 We would just jump to the last question, and we would  
10 be finished, and we would go home early, and some of  
11 us would be very happy.

12 Okay. Why don't we proceed with the  
13 presentation of the new data?

14 DR. HORTON: I'm just a little bit shorter  
15 than Dr. Lipicky.

16 Thank you, Dr. Packer.

17 Good morning. Immediately following the  
18 FDA's recommendation for an additional trial for the  
19 approval of Natrecor, Scios worked closely with the  
20 agency and with many experts in the field to design the  
21 VMAC trial. VMAC is the primary response to the  
22 nonapproval of Natrecor and was designed to  
23 comprehensively address as many of the issue as  
24 possible.

25 The items that I will cover this morning

1 shown on the next slide will be a review of the FDA  
2 concerns and the recommendations, a review of the  
3 Natreacor dose that was selected for the VMAC trial,  
4 and then a detailed discussion of the VMAC trial  
5 design.

6 VMAC stands for vasodilation in the  
7 management of acute congestive heart failure. By the  
8 end of this presentation, you should understand all  
9 aspects of the VMAC trial design and the severity of  
10 illness of the trial population.

11 Next slide.

12 We'll start with the FDA concerns and  
13 recommendations. As you heard from Dr. Lipicky, the  
14 two main reasons for the agency's recommendation for  
15 another trial fell into the two categories of the  
16 pharmacodynamic profile of Natreacor and to expand the  
17 efficacy and safety database.

18 Specifically, the agency was concerned  
19 about the close association and effects on pulmonary  
20 capillary wedge pressure and systolic blood pressure.  
21 This is, of course, a well known association for all  
22 IV vasodilators. So it was important for us to  
23 compare Natreacor to another IV vasodilator, namely,  
24 nitroglycerine.

25 The agency wanted more information on the

1 onset and offset of effects on blood pressure which  
2 were perceived to be slower with Natrecor partly  
3 because of the longer half-life, but also because  
4 there were not enough measurements done early on and  
5 after dose continuation in the previous trials.

6 The agency also questioned whether a fixed  
7 dose regimen for this acute indication would be  
8 appropriate or would be as useful as a titrated  
9 regimen where the doses of another IV vasodilator are  
10 optimized for each patient.

11 The main reasons to expand the safety and  
12 efficacy database primarily were to better  
13 characterize hypertension, especially as it compared  
14 to another IV vasodilator. We were also asked to  
15 confirm the severity of illness and to actually study  
16 patients with symptoms at rest.

17 And finally, a confirmation of the effect  
18 on symptoms was required.

19 The agency's recommendation included both  
20 a placebo control and an active controlled trial, and  
21 that this trial be conducted when these agents are  
22 added to standard care, and the agency also asked that  
23 we study both catheterized and non-catheterized  
24 patients.

25 Other issues that were raised that were

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1 not approval issues per se included the recommendation  
2 that the trial not exclude patients with preserved  
3 systolic function or with active ischemia, but that we  
4 also collect the safety information when Natrecor is  
5 added to other IV vasoactive agents, and that a  
6 prescription for dose adjustments be tested so that  
7 safety information when Natrecor dose is increased  
8 could be obtained.

9 Let's now talk about the dose of Natrecor  
10 that was selected for the VMAC trial. From the NDA,  
11 the largest composite of efficacy and safety  
12 information was for these two doses that Dr. Lipicky  
13 talked about, the .015 and the .03 microgram per kilo  
14 per minute infusion doses. These doses clearly were  
15 associated with dose dependent hemodynamic effects, of  
16 the primary endpoint pulmonary capillary wedge  
17 pressure, and other important hemodynamic variables  
18 shown there.

19 These doses were also associated with  
20 significant symptom improvement in a setting of pure  
21 placebo where IV diuretics had been withheld.

22 But there was also a dose dependent effect  
23 on blood pressure and on the incidence of symptomatic  
24 hypertension. Based on this information, Scios  
25 decided to modify the dose of Natrecor for the VMAC

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1. trial.

2. Next slide.

3. The goal of optimizing the Natrecor dose  
4. was to achieve a more rapid onset of effect and a  
5. better safety profile overall in previously studied  
6. doses. We took advantage of the pharmacokinetics and  
7. pharmacodynamic profiles of Natrecor that were well  
8. characterized in earlier studies at higher doses, and  
9. what we did was we evaluated systematically potential  
10. dosing regimens of Natrecor. This was done by Dr.  
11. Nancy Sanbol at the University of California, San  
12. Francisco, who used a PK/PD model to simulate 24-hour  
13. effects of Natrecor on pulmonary capillary wedge  
14. pressure and systolic blood pressure, and to do this  
15. with candidate regimens of Natrecor.

16. Then each of those candidate regimens was  
17. compared to the .015 microgram per kilo per minute  
18. dose, which was the lowest infusion dose studied in  
19. the Phase III trials.

20. From this modeling, the dose selected for  
21. VMAC was a two microgram per kilo bolus followed by a  
22. fixed dose infusion of .01 micrograms per kilo per  
23. minute. This dosing regimen was chosen because it was  
24. the one that would provide a favorable efficacy and  
25. safety profile.

1           The next slide summarizes the predicted  
2 effects.    The graph on the left summarizes the  
3 predicted effect of VMAC on pulmonary capillary wedge  
4 pressure.  The graph on the right are the effects on  
5 systolic blood pressure.

6           The VMAC dose is represented with a solid  
7 line, and the previous dose, the .015 dose is the  
8 dashed line.

9           You see here that even with the small  
10 bolus that was administered with the .015 dose, the  
11 onset of effect was relatively slow, and the peak  
12 effects were not reached until about four to six  
13 hours.  This was true for both pulmonary capillary  
14 wedge pressure and systolic blood pressure.

15          The model predicted that the VMAC dose  
16 would lead to a peak effect earlier than the  
17 previously studied dose, and that there would be a  
18 sustained effect on pulmonary capillary wedge pressure  
19 over the 24-hour period.

20          The graph on the right, again, shows that  
21 the VMAC dose would achieve a more rapid effect on  
22 systolic blood pressure, but that the overall effect  
23 would be less than that which was observed with the  
24 .015 infusion dose throughout the 24-hour period.

25          As you will see later, the effects

1 predicted by the model were born out by the actual  
2 VMAC data in terms of both efficacy and safety.

3 Let's move on to the VMAC trial design  
4 specifically then.

5 Next slide.

6 After agreement with the agency, the  
7 primary objectives of the trial were to compare the  
8 clinical and hemodynamic effects of Natreacor to  
9 placebo when added to standard therapy. I want to  
10 emphasize that this comparison to placebo for standard  
11 care was primarily to assess efficacy, whereas the  
12 comparison to nitroglycerine was primarily built into  
13 the trial to study safety.

14 The primary endpoints were the three-hour  
15 dyspnea evaluation that was performed by subjects  
16 only, and the primary analysis was done in all  
17 subjects.

18 The other primary endpoint was the three-  
19 hour pulmonary capillary wedge pressure in  
20 catheterized subjects.

21 It's critical to understanding the trial  
22 design to know that the study was powered to show  
23 effects in the dyspnea evaluation in all subjects, not  
24 specifically within the catheterized or non-  
25 catheterized groups.

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1           The protocol specified that both endpoints  
2 had to reach significance with an alpha level at 0.05.  
3 Therefore, no Type 1 error adjustment is needed. This  
4 is actually a much more stringent criteria for  
5 positive study than if there were only one endpoint or  
6 if only one of the two endpoints were needed to reach  
7 significance.

8           The next slide shows the secondary  
9 objectives, which were to compare the clinical and  
10 hemodynamic effects of Natreacor with IV nitroglycerine  
11 when added to standard therapy, again, primarily to  
12 observe the differences in the safety profiles of the  
13 drugs or the similarities.

14           The endpoints of specific interest were  
15 the onset of effect on pulmonary capillary wedge  
16 pressure, the dyspnea evaluation, 24-hour effects on  
17 pulmonary capillary wedge pressure, and the overall  
18 safety profile.

19           Next slide.

20           I'm going to walk you through the VMAC  
21 trial design quickly. We'll then return to the  
22 beginning here and break down each aspect of the trial  
23 design in more detail.

24           The VMAC trial -- could I have the next  
25 slide, please? -- the VMAC trial was a multi-center

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1 trial based at 55 U.S. sites. There were 498 patients  
2 enrolled in the trial over a nine-month period of  
3 time.

4 In response to the request to study both  
5 catheterized and non-catheterized patients, the study  
6 used a stratified randomization based on the  
7 investigator's clinical decision of whether the  
8 patient required a right heart catheter for the  
9 physician to better manage their decompensated heart  
10 failure.

11 In a few minutes I'll describe the reasons  
12 that patients were catheterized and some of the  
13 differences between the catheterized and the non-  
14 catheterized populations.

15 Next slide.

16 In the non-catheterized stratum, patients  
17 were randomized to three treatment groups:  
18 nitroglycerine, placebo, and Natrecor fixed dose.

19 Next slide.

20 In the catheterized stratum, patients were  
21 randomized to the same three treatment groups with the  
22 addition of a fourth group, the Natrecor adjustable  
23 dose group.

24 This study was double blinded throughout,  
25 and during the first three hour double blinded period,

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1. symptoms, hemodynamics and vital signs were frequently  
2 collected during the first three hours.

3 Dr. Young will later show you that  
4 Natrecor added to standard care significantly improved  
5 both pulmonary capillary wedge pressure and dyspnea  
6 compared to placebo plus standard care at three hours.

7 After this double blinded period -- next  
8 slide -- placebo patients were crossed over to active  
9 therapy, double blinded active therapy, with either  
10 Natrecor or nitroglycerine -- I'm sorry -- either  
11 nitroglycerine or Natrecor fixed dose. This occurred  
12 in both catheterized patients, as well as non-  
13 catheterized patients.

14 The crossover to active therapy was done  
15 to add to the total safety experience and the  
16 comparisons between Natrecor and nitroglycerine. The  
17 total duration of study drug was left to the  
18 investigator's discretion, and patients were followed  
19 for six months to collect mortality.

20 Let's now go back to the beginning of the  
21 trial design schema to explain in more detail several  
22 aspects of the trial design.

23 Who were the VMAC patients?

24 Why were they catheterized?

25 And what were some of the differences

1 between the catheterized and on-catheterized patients?

2 Next slide.

3 Well, the study aimed to enroll the  
4 sickest patients with decompensated heart failure by  
5 limiting enrollment only to those with dyspnea at rest  
6 or Class IV symptoms at presentation. Patients had to  
7 require hospitalization and IV therapy for acutely  
8 decompensated CHF. They also, of course, had to have  
9 heart failure as the primary cause for the dyspnea.

10 And finally, patients had to have solid  
11 clinical evidence of elevated cardiac filling  
12 pressures either by clinical estimate in non-  
13 catheterized patients or by a measured pulmonary  
14 capillary wedge pressure of at least 20 millimeters of  
15 mercury in catheterized patients.

16 Next slide shows the exclusion criteria,  
17 and the VMAC trial design had very few exclusion  
18 criteria in order to enroll the broadest possible  
19 population of acute decompensated heart failure  
20 patients. Patients with a baseline systolic blood  
21 pressure of less than 90 were excluded because this  
22 was a head-to-head comparison against two IV  
23 vasodilators.

24 For the same reason, patients with volume  
25 depletion or cardiogenic shock were also excluded.

1 Those receiving IV nitroglycerine that could not be  
2 withheld were excluded because of the head-to-head  
3 comparison against nitroglycerine.

4 And finally, patients who were  
5 mechanically ventilated were excluded because each  
6 patient had to independently assess their own dyspnea  
7 score.

8 Important patient subsets that were not  
9 excluded in the trial were those with acute coronary  
10 syndromes, significant atrial or ventricular  
11 arrhythmias, any degree of renal insufficiency,  
12 preserved systolic function, and the elderly.

13 Now let's look at the demographic  
14 characteristics and medical history of the VMAC  
15 patients. The VMAC trial population was a typical  
16 acutely ill heart failure population that included  
17 many minorities and female patients. The mean age was  
18 62 years, and 43 percent of the population was at  
19 least 65 years of age.

20 Nearly 40 percent of the trial population  
21 were minorities, and nearly a third were women.

22. Next slide.

23 Most patients had ischemic cardiomyopathy,  
24 with 65 percent of them having documented coronary  
25 artery disease, and almost half having a history of a

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1 previous myocardial infarction. Seventy percent had  
2 a history of hypertension, and almost half had a  
3 history of diabetes.

4 Many of the patients also had significant  
5 arrhythmias, such as atrial fibrillation and ICD or  
6 pacemaker in place and life threatening ventricular  
7 arrhythmia shown on the slide.

8 Next slide.

9 The medications that these patients were  
10 taking before entry into the study were typical for a  
11 population with advanced CHF. Ninety-five percent  
12 were taking diuretics, and there was another 26  
13 percent that was taking spiral lactone. Almost 70  
14 percent were taking digoxin and ACE inhibitors, and  
15 another 11 percent were taking an A-2 receptor  
16 antagonist. Almost half also had non-IV nitrates  
17 added to ACE inhibitors, and 39 percent were taking a  
18 beta blocker before entry into the trial.

19 Of course, there were no restrictions on  
20 any of these medications, and they could be continued  
21 at any time point as clinically indicated.

22 Next slide.

23 Sixty-one patients in the trial had an  
24 acute coronary syndrome associated with their  
25 decompensated CHF. Most patients had systolic

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1 dysfunction, and the mean ejection fraction was 27  
2 percent. Fifteen percent of the population had  
3 relatively preserved diastolic function defined as an  
4 ejection fraction of greater than 40.

5 It's worth noting that none of the earlier  
6 Phase III trials actually excluded patients with  
7 preserved systolic function. However, the ejection  
8 fraction was not collected in those trials.

9 Baseline hemodynamics were consistent with  
10 a population with a compensated CHF. In the  
11 catheterized group, the mean pulmonary capillary wedge  
12 pressure was 28 millimeters of mercury; mean cardiac  
13 index was 2.2 liters per minute per meter squared.

14 Mean systolic blood pressure was  
15 approximately 120 millimeters of mercury. However,  
16 about 20 percent of patients had a mean blood pressure  
17 less than 100, and another approximately 20 percent  
18 were hypertensive with a mean blood pressure of great  
19 than 140.

20 Again, this shows the heterogeneity of the  
21 VMAC population.

22 Next. I'm sorry.

23 There were no restriction of patients  
24 based on any baseline laboratory parameters, and you  
25 can see here that the mean baseline creatinine was 1.6

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1. milligrams per deciliter, with a range of up to 11  
2 millimeters of per deciliter.

3                   Twenty-one percent of the population had  
4 a mean creatinine that was at least two milligrams per  
5 deciliter, all of this showing that this was a  
6 population that had significant renal insufficiency at  
7 baseline.

8                   So why were the VMAC patients  
9 catheterized? On the next slide, you see that as  
10 expected, in most patients the investigator identified  
11 several reasons that a right heart catheter was used.  
12 The most common reason was uncertain hemodynamics in  
13 83 percent of the patients. This was also identified  
14 as the primary reason in a little more than half of  
15 the patients.

16                   The next most common reasons were  
17 suspected low cardiac output or to optimize out-  
18 patient medications in approximately half of these  
19 patients.

20                   Other reasons included potential  
21 transplant candidate, significant renal dysfunction,  
22 and a low or unstable blood pressure.

23                   There were important clinical differences  
24 between the catheterized or non-catheterized subject,  
25 and that is described on the next slide. More

1 catheterized subjects were men, and this correlates  
2 with the fact that more of the men had ischemic  
3 cardiomyopathy and lower ejection fractions. More  
4 catheterized patients did have ischemic  
5 cardiomyopathy, whereas more of the non-cath. patients  
6 tended to have hypertensive cardiomyopathy.

7 Patients with acute coronary syndromes  
8 tended to be managed without a right heart catheter.

9 Catheterized patients had worse systolic  
10 function, and not surprisingly, patients with  
11 preserved systolic function tended to be managed  
12 without a right heart catheter.

13 Mean blood pressure was somewhat lower,  
14 significantly lower, and then finally, possibly due to  
15 the worst systolic function in the catheterized group,  
16 the catheterized patients tended to have more  
17 significant arrhythmias as shown here.

18 Now let's talk about study drug and  
19 background therapies. One of the more critical trial  
20 design features of VMAC is that study drug was added  
21 to standard care. This differs significantly from the  
22 previous pivotal trials that Dr. Lipicky showed you  
23 earlier in which IV diuretics and chronic therapies  
24 were withheld for a period of time before the start of  
25 study and during the placebo controlled period.

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1                   So VMAC sought to demonstrate the added  
2 benefit of Natreacor when added to standard therapies  
3 by having no restrictions on the use of IV or oral  
4 diuretics, ongoing therapy with dobutamine or dopamine  
5 at baseline, and the use of any chronic cardiac  
6 medications.

7                   Medications that were restricted included  
8 the IV nitrates and Milrinone for the reasons I  
9 already described.

10                   For nitroglycerine dosing, the initial  
11 dose and any titration of nitroglycerine was entirely  
12 left to the investigator's discretion as there is no  
13 standard dose for nitroglycerine for acute  
14 decompensated heart failure patients. Investigators  
15 were instructed to use nitroglycerine as they  
16 typically do and to actively titrate nitroglycerine to  
17 clinical effect.

18                   The Natreacor fixed dose group received the  
19 dose I described earlier to you, the two microgram per  
20 kilo bolus, followed by the 0.01 microgram per kilo  
21 per minute infusion.

22                   The Natreacor adjustable dose received the  
23 same dose as the fixed dose for the first three hours,  
24 that is, all adjustable dose patients started out with  
25 the same bolus in infusion because any adjustments of

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1 Natrecor could not actually be made until after the  
2 three-hour primary endpoints were obtained.

3 After three hours, adjustments could only  
4 be made every three hours incrementally to a maximum  
5 of 0.03. I'll tell you a little bit more about that  
6 in a couple of slides.

7 Now, in order to conduct a placebo and  
8 active controlled study comparing a fixed dose regimen  
9 to a titratable regimen, a double dummy study drug  
10 administration design was used.

11 The next slide.

12 This portrays a graphic of what patients  
13 actually received. Each patient received two  
14 simultaneous infusions throughout the duration of  
15 study drug labeled as nitroglycerine-placebo and  
16 Natrecor-placebo. Investigators were instructed to  
17 manage the dosing of each infusion as if each infusion  
18 contained active drug.

19 In reality each patient received either  
20 placebo plus placebo, nitroglycerine plus placebo, or  
21 placebo plus Natrecor.

22 Of course, if study drug needed to be  
23 decreased or discontinued, both study drug infusions  
24 were to be decreased or discontinued simultaneously.

25 So how was each drug to be administered?

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1 Well, nitroglycerine-placebo was to be  
2 actively titrated, as I already mentioned, with the  
3 initial dose and any dose adjustments entirely left to  
4 the investigator's discretion.

5 What about Natreacor-placebo?

6 Next slide.

7 In all nine catheterized patients, the  
8 only Natreacor regimen that they received was Natreacor  
9 fixed dose. So this was the set-up that they had:  
10 nitroglycerine-placebo and a Natreacor-placebo bag that  
11 was labeled as fixed dose.

12 Since this dose could not be increased, it  
13 was pretty simple. The only dose that could be  
14 titrated and actively titrated was nitroglycerine.

15 Okay. In catheterized patients, there  
16 were the two treatment groups of fixed dose and  
17 adjustable dose. So in order to maintain the blinding  
18 of fixed dose and adjustable dose, these two labels,  
19 fixed dose label and adjustable dose label, were  
20 equally distributed among all catheterized patients  
21 regardless of treatment group.

22 So half of all catheterized patients had  
23 this set-up and half had this set-up.

24 Now, during the first three hours of  
25 infusion, I mentioned to you that no adjustments could

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1 be made. So in spite of the two labels, it was  
2 actually pretty simple because even if you had an  
3 adjustable dose label, no adjustments could be made.  
4 So all patients received fixed dose Natrecor.

5 Now, after the first three hours, I'll  
6 give you a little information on how adjustments of  
7 Natrecor were to be made if clinically indicated.

8 Next slide.

9 Natrecor-placebo adjustable dose could  
10 only be increased if it was clinically indicated, and  
11 secondly, if the .01 infusion that had been  
12 administered for at least three hours was well  
13 tolerated. We specifically required that systolic  
14 blood pressure needed to be at least 100 millimeters  
15 of mercury and that wedge was at least 20 millimeters  
16 of mercury in the protocol.

17 Dose increases could be done no more  
18 frequently than every three hours, and they were  
19 optional. To incrementally increase the dose, a one  
20 microgram per kilo bolus was administered followed by  
21 an increase in the infusion by .005 micrograms per  
22 kilo per minute. So a patient would go from .01 to  
23 .015, three hours later, .015 to .02 if necessary.  
24 And the maximum dose, as I stated, was .03.

25 Lastly, due to the double dummy study

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1 design when Natrecor-placebo dose was increased, it  
2 made sense that nitroglycerine-placebo should also be  
3 increased, and similarly increases in nitroglycerine  
4 should be associated with an increase in adjustable  
5 dose Natrecor.

6 Now let's talk about the primary  
7 endpoints. First, why were the primary endpoints  
8 collected at three hours? Well, many of you helped  
9 designing these clinical trials know that this  
10 particular point is often difficult to decide, but due  
11 to the expected severity of illness of these patients  
12 with dyspnea at rest, it was felt that the placebo  
13 controlled period could not be longer than three  
14 hours.

15 However, at least three hours were  
16 required to adequately assess the onset of effect and  
17 the time to peak effects compared to placebo.

18 So what happened at the three-hour time  
19 point? Well, in all patients, the first thing that  
20 was done was that their self-assessment of dyspnea and  
21 global assessment was obtained. In a moment I'll  
22 discuss the symptom assessment in more detail.

23 In catheterized patients then, a wedge  
24 pressure was obtained. The primary endpoint  
25 measurements were then entered onto a work sheet by

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1 the study staff, and then a telephone call was made by  
2 the study staff, and the primary endpoint data were  
3 actually entered into the central randomization  
4 system. Okay?

5 The dyspnea global assessment and wedge  
6 results were entered into the system, and at that time  
7 the study staff was told whether the patient had been  
8 receiving placebo or active therapy.

9 If they were receiving active therapy,  
10 knowledge of whether they were receiving Natrecor or  
11 nitroglycerine was not revealed.

12 This step of entering the data into the  
13 central telephone system was important to help  
14 guarantee, first, that the primary endpoints were  
15 obtained and, secondly, that they were obtained before  
16 unblinding.

17 Then a fax confirming that this call had  
18 been made was sent to the pharmacist from the central  
19 randomization center to signal to the pharmacist to  
20 send down the second set of infusions for placebo  
21 patients who were to cross over to standard care, and  
22 once the new sets arrived, the patients crossed over  
23 to active therapy. If they were an active therapy  
24 patient, the original infusions were simply continued.

25 Now, let's talk about the symptom

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1 assessment itself. Based on input from this Committee  
2 two years ago and by the agency, there was some  
3 concern that a physician assessment could bias a  
4 patient's own assessment of their symptoms. To avoid  
5 as much bias as possible, symptoms were only assessed  
6 by the patient in the VMAC trial.

7 The patient filled out a symptom work  
8 sheet independently and the staff was instructed not  
9 to assist the patient or discuss their assessments  
10 with them.

11 This environment in which VMAC was  
12 conducted is very important for you to understand  
13 because all of the staff, the study  
14 coordinators, and even any ancillary staff were  
15 instructed if this was a VMAC patient, you're not to  
16 be discussing the patient's clinical status with them.

17 Then in catheterized patients  
18 specifically, the work sheet was completed before the  
19 hemodynamics were measure, and the hemodynamics,  
20 again, were not to be discussed with the patient.

21 Next slide.

22 The key to this assessment, given that  
23 this was a very sick population that was having  
24 trouble breathing, the assessment needed to be able to  
25 be filled out quickly, and it really needed to be very

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1 simple.

2 Patients were asked: compared to how much  
3 difficulty you were having breathing just before study  
4 drug was started, how is your breathing now? And then  
5 patients were asked to mark off one of these seven  
6 choices ranging from markedly better to no change to  
7 markedly worse, and then each patient signed and dated  
8 and timed their assessment.

9 Okay. Let's talk now about the  
10 documentation of symptomatic hypotension. Consistent  
11 and complete documentation of symptomatic hypotension  
12 events was also critical to the design of the trial.  
13 The protocol stipulated that whenever symptomatic  
14 hypotension occurred, the following data were  
15 collected.

16 First, the start time of the first  
17 symptom, the time of any dose changes that might have  
18 occurred, all symptoms that were considered to be  
19 associated with the decreases in blood pressure, and  
20 the predominant symptoms was noted.

21 It was also noted whether the patient  
22 volunteered the symptom or whether it was elicited by  
23 the staff, and then, of course, the last time -- the  
24 time of the last symptom resolution was also recorded.

25 In addition, frequent blood pressure

1 measurements were mandated by the protocol after the  
2 onset of symptomatic hypotension. Specifically, blood  
3 pressure was measured every 15 minutes for the first  
4 hour, then every 30 minutes for the second hour, and  
5 in addition to that, every 30 minutes if blood  
6 pressure had not stabilized above 90 millimeters of  
7 mercury.

8 The next slide then summarizes other  
9 endpoints that were collected after the three-hour  
10 primary analysis. Again, given the importance of  
11 describing the onset and offset of effect on blood  
12 pressure, frequent blood pressure measurements were  
13 obtained after the start of study drug to look at the  
14 onset and after any dose reduction or discontinuation  
15 to look at the offset effect.

16 To assess the sustained effects of the  
17 drug, PCWP and pulmonary artery pressures were  
18 obtained through at least 24 hours and through 48  
19 hours in patients who still had a right heart  
20 catheter.

21 The global assessment was also obtained in  
22 addition to the dyspnea assessment. Readmissions for  
23 30 days were collected. Daily creatinines during the  
24 hospitalization, and patients also came back at day 14  
25 and day 30 if necessary for an additional creatinine.

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1                   And finally, six-month mortality was  
2 noted. It's worth mentioning here that mortality was  
3 not a nonapproval issue, nor was there any guidance on  
4 the sample size of the VMAC trial in order to answer  
5 any mortality questions.

6                   During the early ramp-up phase of VMAC, it  
7 was mentioned by the agency that we should collect  
8 six-month mortality and some additional information  
9 was emerging with other agents. So this was early in  
10 the ramp-up phase, and the protocol was amended, and  
11 we did collect six-month mortality prospectively.

12                   However, VMAC is not a mortality trial and  
13 did not include design features that would be typical  
14 of a mortality trial.

15                   Okay. The next slide.

16                   Because VMAC was a double dummy study  
17 throughout the six-month period, we did use a data  
18 safety monitoring committee that periodically reviewed  
19 unblinded safety data. The committee was chaired by  
20 Dr. Cody. Other members included Dr. Colucci, Dr.  
21 Fleming, and Dr. Massie.

22                   Next slide.

23                   The focus of their review was on these  
24 four pre-specified safety endpoints that were listed  
25 in the protocol: death, myocardial infarction,

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1 stroke, and acute renal failure requiring dialysis.

2 However, the committee also reviewed all  
3 details of episodes of symptomatic hypotension and all  
4 serious adverse events with clinical narratives, and  
5 then the pulmonary capillary wedge pressure at three  
6 hours.

7 Next slide.

8 So here we are again, back to our summary  
9 of the issues that were addressed by the VMAC trial.  
10 We conducted this double blinded comparison to the  
11 placebo and IV vasodilators when these drugs were  
12 added to standard care.

13 Design features were added to address the  
14 remaining questions relative to the pharmacodynamic  
15 profile and to those that pertain to additional  
16 efficacy and safety data that would be obtained with  
17 a larger study.

18 And lastly, additional safety questions  
19 related to special patient populations, dose  
20 adjustments of Natreacor, and the concomitant use of  
21 Natreacor with dobutamine or dopamine was collected.

22 In summary -- next slide -- with the  
23 addition of VMAC and one other study called the  
24 PRECEDENT trial, which I'll briefly describe to you  
25 later, 442 Natreacor patients have been added to the

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1 NDA for a total of 941 patient exposures to Natrecor.  
2 The total clinical program includes almost 1,600  
3 patients.

4 Also, the NDA can now be reconsidered with  
5 comparative data to a commonly used IV vasodilator,  
6 nitroglycerine, and a commonly used xenotrope,  
7 dobutamine.

8 Thank you for your attention.

9 I'd now like to ask Dr. Young to come up  
10 if there's no questions.

11 CHAIRMAN PACKER: Dr. Horton, why don't  
12 you stand by?

13 DR. HORTON: Okay.

14 CHAIRMAN PACKER: And we'll take questions  
15 from the Committee. Let me ask the Committee to  
16 restrict their questions to the topics presented by  
17 Dr. Horton.

18 We'll obviously get more information on  
19 VMAC subsequently. So hold your questions on the  
20 results, and we'll start with our primary reviewer,  
21 Dr. Pina.

22 DR. PINA: Good morning.

23 DR. HORTON: Good morning.

24 DR. PINA: A very nice presentation.

25 I continue to be confused with the double

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1 dummy. Particularly let's say that the patient has  
2 been randomized to the adjustable dose. This is now  
3 the catheterized group. How were they instructed to  
4 increase the dose?

5 I would imagine of the investigators  
6 standing by the bedside and they're looking at the  
7 wedge. They're going to want to lower the wedge to a  
8 certain level. So which of the two bottle or bag did  
9 they start with to make an adjustment?

10 DR. HORTON: Well, after the three-hour  
11 primary endpoints were measured, then the physicians  
12 made their assessment of the patient as they normally  
13 would whether they were catheterized or not. Of  
14 course, they did have knowledge of the hemodynamics.

15 So it was entirely left up to the  
16 investigator. If they decided that it was clinically  
17 indicated that further vasodilation would be  
18 beneficial for this patient, then they were then given  
19 the prescription for how they would adjust the  
20 Natreacor dose, which was the smaller bolus and the  
21 small increase in the infusion to .015.

22 And at that time, they should have made an  
23 increase in the nitroglycerine dose or maybe recently  
24 had made an increase in the nitroglycerine dose since  
25 there was a time constraint on when they could adjust

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1 Natrecor, but not nitroglycerine.

2 DR. PINA: So the nitroglycerine could  
3 have been adjusted at any time?

4 DR. HORTON: Yes. Nitroglycerine  
5 adjustments, there were no restrictions placed by the  
6 protocol on how one would optimally used  
7 nitroglycerine.

8 DR. PINA: All right. When you made the  
9 -- when you put up the demographics of the patients,  
10 I didn't see you put up the New York Heart class.  
11 Does that mean that by definition everybody was Class  
12 IV?

13 DR. HORTON: By definition at presentation  
14 all patients were Class IV. That's correct. All  
15 patients had dyspnea at rest at presentation, and that  
16 was the most critical part of the inclusion criteria  
17 for this population.

18 DR. PINA: Because we have a table here  
19 that has been provided by the agency that talks about  
20 the New York Heart class prior to admission, and  
21 there's a number of Class IIs and IIIs in there.

22 DR. HORTON: Yes. We also did collect,  
23 and when we specifically ask people to rate people's  
24 New York Heart Association class prior to this  
25 exacerbation, so basically their level of debility

1 while at home before this exacerbation. And we do  
2 have that information.

3 You can see there that about 85 percent of  
4 the patients had either Class III or Class IV. In the  
5 45 percent range had Class IV symptoms even when they  
6 were controlled at home.

7 DR. PINA: So this is all prior to this  
8 event that brought them in?

9 DR. HORTON: Yes, yes.

10 DR. PINA: Dealing with the definitions of  
11 hypotension, did anybody do any orthostatics on the  
12 patients at any time?

13 DR. HORTON: We did not mandate that, but  
14 there were times when orthostatics were collected, and  
15 we did ask for the site to, as they listed the adverse  
16 event, to state whether it was an orthostatic event or  
17 not. But we included all of that as symptomatic  
18 hypotension.

19 DR. PINA: I have no other questions on  
20 that presentation.

21 CHAIRMAN PACKER: We'll go on to Jeff and  
22 then Ralph and many others, I assume.

23 DR. BORER: I'd appreciate just a little  
24 more clarification on the double dummy set-up and the  
25 blinding that Ileana asked you about. If I understand

1 correctly, if someone was actually receiving Natrecor,  
2 they would have a placebo in the nitroglycerine bag  
3 and would be dialing up placebo, which they could do  
4 at any time. Is that it?

5 DR. HORTON: Correct.

6 DR. BORER: Okay, and if they were on  
7 placebo, then there were placebos in both bags.

8 DR. HORTON: Correct.

9 DR. BORER: Now, I am familiar with a  
10 study that Jay Cohn did when he did the first V-HEFT  
11 where he found that doctors were right in predicting  
12 whether they were on active vasodilator IV or placebo  
13 exactly 50 percent of the time. So I guess this is  
14 reasonable.

15 But, you know, did anybody do any thinking  
16 about the likelihood of unblinding in a situation  
17 where the doctors were looking at pressures when they  
18 were -- when anyone was assessing symptoms?

19 DR. HORTON: Well, there were two  
20 populations, the catheterized and non-catheterized,  
21 and in the catheterized group, we did not ask them  
22 what they thought the patient was on. It may have  
23 been interesting had we done that.

24 but, you know, this was a typical  
25 hospitalized situation where obviously they knew the

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1 hemodynamics because they were also actively titrating  
2 nitroglycerine to effect supposedly.

3 CHAIRMAN PACKER: Ralph.

4 DR. D'AGOSTINO: I enjoyed your  
5 presentation very much, and it's nice actually that  
6 you give the design and then not immediately the  
7 results so that I can squeeze in some questions on how  
8 you thought about the analysis.

9 With the primary endpoint of shortness of  
10 breath, I'm a bit confused. You have this dichotomy  
11 of catheterized versus non. Yet your analysis is  
12 going to be on all subjects, and is it just a power  
13 problem? And should we be looking at the similarities  
14 within the catheterized and non-catheterized?

15 I mean, is there any reason a priori to  
16 think there's going to be a difference in those two  
17 groups in terms of shortness of breath?

18 DR. HORTON: Well, the reason why we  
19 collected them both in hemodynamically monitored  
20 patients, as well as non-hemodynamically monitored  
21 patients partly was to address this question of  
22 whether there was, indeed, hemodynamic bias, and I  
23 think you'll find the data interesting.

24 But it was a power issue, but it wasn't  
25 just based on -- the power calculations were not

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1 necessarily based on good estimates from any other  
2 trials that had been done, and even our previous  
3 trials were only somewhat helpful in estimating what  
4 the sample size should be because a significant  
5 difference between this trial and the previous ones  
6 were that IV diuretics were allowed, and everyone  
7 knows that patients get better when they get IV  
8 diuretics.

9 So I think the agency and Scios agreed  
10 that it would be okay to pre-specify the primary  
11 endpoint with both populations because the trial was  
12 large enough we had an additional 246 non-catheterized  
13 patients included in the primary analysis.

14 DR. D'AGOSTINO: Another question. You  
15 talk about the nitroglycerine, and you say it's for  
16 safety. Does that mean I shouldn't be concerned about  
17 the nitroglycerine versus placebo comparisons on  
18 efficacy?

19 DR. HORTON: That you should not be  
20 concerned with?

21 DR. D'AGOSTINO: With the nitroglycerine  
22 versus placebo comparisons on the efficacy.

23 DR. HORTON: I think it's fair game. You  
24 can be concerned with the nitroglycerine versus  
25 placebo comparisons.

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1 DR. D'AGOSTINO: And what if they turn out  
2 not to be significant? I mean should I worry about it  
3 if they didn't turn out to be significant? I'm  
4 interested in why you focused that. You said it was  
5 only for safety as opposed to some sort of validity of  
6 the study or something like that, or sensitivity.

7 DR. HORTON: Well, I think the totality of  
8 the data need to be taken into context on what is  
9 known about nitroglycerine, why people use  
10 nitroglycerine, and what the expected effects are.

11 DR. D'AGOSTINO: And just two more brief  
12 questions. You have a lot about the severity of  
13 illness. I see you're bringing in, again, in response  
14 to the FDA, a number of very sick individuals,  
15 diabetics, hypertensives, coronary artery disease, and  
16 so forth, and it's anticipated that -- it's a  
17 question. Is it anticipated that the effect would be  
18 the same and then subset analysis would just be a way  
19 of seeing a differential effect in these different  
20 groups?

21 I mean the reason they -- I understand the  
22 reason is that they wanted to make sure that you do,  
23 in fact, have sick individuals in the sample. Now my  
24 question is when you do that, you've got such an  
25 heterogeneous group of individuals, how should I look

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1 at those individuals?

2 DR. HORTON: Yeah, I think that's typical  
3 when you're looking at, you know, a heterogeneous  
4 population, and so, of course, the primary interest is  
5 the primary analysis, but we do have some subgroups  
6 that we can give you some data about.

7 I mean, primarily the information that was  
8 really necessary, including your subgroups for safety  
9 information, we'll be able to show that, too.

10 DR. D'AGOSTINO: And just one last  
11 question. Your primaries are three hours.

12 DR. HORTON: Yes.

13 DR. D'AGOSTINO: But you follow these  
14 individuals. You have the sustained effect, and so  
15 forth. I mean, if that all fell apart, would the  
16 primary carry the day? What am I doing with these  
17 other sets of analysis?

18 DR. HORTON: Well, I think, you know, when  
19 you're measuring lots of endpoints, then it comes down  
20 to picking a primary endpoint and pre-specifying it  
21 just because of what you're showing.

22 DR. D'AGOSTINO: Is there a logic to it?  
23 I mean is it --

24 DR. HORTON: Is there logic to it?

25 DR. D'AGOSTINO: In the sense of would the

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1 sustained be more important than the three hours?

2 DR. HORTON: I'm going to ask you that  
3 question.

4 DR. D'AGOSTINO: Well, I mean, is the only  
5 reason you're picking the three hours because the  
6 statisticians on the Committee say that you need to  
7 pick a primary, or is it really the ensemble that we  
8 should be worried about?

9 DR. HORTON: Well, that's really a  
10 philosophical question, but clearly in our discussions  
11 with the FDA and with us in designing the trial, it's  
12 always been quite important to just pick a primary  
13 endpoint and stick to it.

14 The other thing I would like to add about  
15 your question about the cath. versus the non-cath.  
16 group is that even though we pre-specified that the  
17 primary endpoint for dyspnea was in both groups, we  
18 did test the interaction to make sure that it would  
19 still be valid to do the primary analysis, and there  
20 was no interaction on dyspnea between cath. and non-  
21 cath. patients. That was insignificant.

22 DR. D'AGOSTINO: Thank you.

23 DR. HORTON: Thank you.

24 DR. NISSEN: I had a question for you  
25 about the instructions to the investigators when

1 titration was taking place. If they were to -- in the  
2 catheterized patients if they saw, let's say, a high  
3 wedge pressure, they then would titrate both bags; is  
4 that correct?

5 DR. HORTON: Well, most of the patients  
6 were fixed dose, right? Because only half of the  
7 catheterized patients and all of the non-cath.  
8 patients were fixed dose. So most were fixed dose.  
9 So in that case, you're describing the situation where  
10 the wedge is known.

11 DR. NISSEN: Yeah, yeah.

12 DR. HORTON: So if they were a patient  
13 that had an adjustable dose label, then they would go  
14 up on both bags.

15 Now, remember that the placebo in  
16 nitroglycerine patients may have also had an  
17 adjustable dose label, but during the three-hour time  
18 point, this is actually not the case. I'm getting  
19 confused myself.

20 During the three-hour time point, no  
21 adjustments in the adjustable dose could be made. The  
22 labels were there to continue the blind through the  
23 three-hour period even though no adjustments could be  
24 made.

25 DR. NISSEN: But in those patients in whom

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1 an adjustment was to be made --

2 DR. HORTON: Right.

3 DR. NISSEN: -- a simultaneous adjustment  
4 of both bags was the instruction?

5 DR. HORTON: Well, it depended on if an  
6 adjustment of Natrecor had previously been made.

7 DR. NISSEN: Yes.

8 DR. HORTON: If no adjustment had been  
9 made, then at the time that an adjustment could have  
10 been made, then, yes, both infusions would be made.  
11 If already a Natrecor dose had been increased, say, an  
12 hour ago and for some reason, you know, they wanted to  
13 go up on the dose again, they could go up on  
14 nitroglycerine, but they couldn't go up on Natrecor  
15 until two hours later because the prescription was  
16 that the adjustments could only be made every three  
17 hours.

18 DR. NISSEN: And then a secondary question  
19 is: was there a maximum specified dose of IV  
20 nitroglycerine? Could they give 1,000 microgram is  
21 they wanted?

22 DR. HORTON: They could. There was no  
23 maximum.

24 DR. NISSEN: Okay.

25 DR. LINDENFELD: In the same vein, I'd

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1 like to have a little more information about the  
2 investigator's use of nitroglycerine. You that it was  
3 left up to each investigator, but was each  
4 investigator asked over the course of the study to  
5 have a specific goal?

6 In other words, were there any goals in --  
7 what I'm getting at here is was one patient treated  
8 differently than another. Was there a 25 percent  
9 reduction in WED (phonetic) to a ten percent increase  
10 in cardiac output? And was there any consistency in  
11 how that was done?

12 DR. HORTON: Right. There were no  
13 instructions in that regard, and this was actually the  
14 result of lots of discussions with lots of experts,  
15 and we realized that whatever recommendation was made  
16 would have limitations for some reason or another.

17 But the other main reason why we did not  
18 give instructions is that the worst thing that could  
19 happen, we thought, was that nitroglycerine might be  
20 under dosed, and since this was a safety study, then  
21 you'd be comparing Natrecor against either, you know,  
22 optimal doses of nitroglycerine or low doses, but we  
23 didn't want to bias the study towards Natrecor by  
24 telling the investigators to up-titrate nitroglycerine  
25 with any criteria because the primary goal of that was

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1 to do safety, and we didn't want to be here today, you  
2 know, worried about us having favored the study  
3 towards Natrecor by instructing investigators to  
4 aggressive titrate nitroglycerine.

5 DR. LINDENFELD: I think we'll come back  
6 to this issue of under dosing, but I think it is under  
7 dosed.

8 DR. HORTON: You'll see. You'll learn a  
9 lot about that, yes.

10 DR. LINDENFELD: And then I want to go  
11 back to the modeling you said about the dose of  
12 Natrecor.

13 DR. HORTON: Yes.

14 DR. LINDENFELD: It's my understanding  
15 that you modeled the dose to avoid hypotension.

16 DR. HORTON: We modeled the dose -- there  
17 were two aspects of it. The first was selection of  
18 the bolus to achieve a more rapid onset of effect, and  
19 that was to deal with the question of whether this  
20 drug was useful in an acute setting.

21 The second aspect of it was the infusion  
22 dose, and there were two parts to that: because we  
23 wanted to lower the dose to reduce the possibility of  
24 hypotension, but we wanted to still have an effective  
25 dose and one that would have sustained wedge effects

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1 over 24 hours.

2 DR. LINDENFELD: And the sustained wedge  
3 effect you wanted to have was? What was the target?

4 DR. HORTON: It wasn't based on a target  
5 actually. It was just based on what we knew about the  
6 sustained PK data and sustained hemodynamic effects  
7 from the previous studies. You know, clearly this was  
8 a model and this was how we selected the dose, but  
9 there wasn't any specific criteria, and then the  
10 trial, the data are what really well tell you how that  
11 works out.

12 CHAIRMAN PACKER: Tom.

13 DR. GRABOYS: That was an excellent  
14 presentation. I think you certainly covered all of  
15 the bases. I'm just curious about the percentage of  
16 patients who were screened in, and then the number of  
17 patients who were screened out, some numbers on that,  
18 and whether or not there's any data.

19 DR. HORTON: Right.

20 DR. GRABOYS: I'm interested about the  
21 folks who were screened out.

22 DR. HORTON: We did maintain -- yeah,  
23 pardon me. We did maintain screen logs, but I don't  
24 have that data summarized.

25 DR. GRABOYS: So you don't have a ballpark

1 about whether -- I mean were there X thousands  
2 screened and you excluded --

3 DR. HORTON: No, I don't know. A thousand  
4 sounds like a lot, but I mean, I don't know.

5 CHAIRMAN PACKER: Yeah, I must say that as  
6 just a comment on screening logs, lots of sponsors ask  
7 for screening logs. I have no idea what they ever do  
8 with that information.

9 (Laughter.)

10 CHAIRMAN PACKER: I have no idea how  
11 investigators are supposed to fill out screening logs.  
12 You know, it's sort of an interesting quirk of how we  
13 do clinical trials. We know that the people that are  
14 enrolled in clinical trials are selected, and I guess  
15 their screening logs are an attempt to determine how  
16 selected they were, but I'm not certain that it  
17 represents an adequate tool because then there's bias  
18 in how the screening log is filled out.

19 So, well, it's sort of an interesting  
20 quirk of how we do trials, but I'm glad you brought it  
21 up because I don't know how -- I don't know what would  
22 have been the right answer. I'm not certain there was  
23 one.

24 DR. HORTON: No, actually I'd like to just  
25 make another comment on that because what was

1 discussed in great detail with the sites was to  
2 minimize the time between screening randomization and  
3 start of study drug because these patients had dyspnea  
4 at rest, and we were not restricting the use of  
5 standard care therapies. So we really didn't want  
6 patients that were identified with dyspnea at rest in  
7 the emergency room, got diuretics, and then they maybe  
8 didn't get study drug for six hours, and by that time  
9 they didn't have dyspnea at rest because the primary  
10 endpoint was dyspnea at rest.

11 So although I don't have any numbers, I  
12 think given that, you know, this is a screening  
13 population where you would already be selective  
14 because you're limiting it to those who had dyspnea at  
15 rest, which is, of course, the majority of the  
16 patients, but also there's not a whole slew of  
17 restriction criteria that are going to allow you to  
18 knock people out for one reason or another.

19 That's the only other insight I can give  
20 you on that.

21 DR. HIRSCH: Well, maybe I'll pursue that  
22 one more moment because I had sort of the same  
23 question. I mean, a screening log sometimes helps a  
24 bit because you want to know the characteristics of  
25 the population now so that if I apply this in the

1 community hospital, am I apply this to my average  
2 older woman coming into the emergency room or am I  
3 applying this only to people coming out of the cath.  
4 lab with a positive component?

5 So I'm curious. So let me pursue that a  
6 step further.

7 The acute coronary syndrome population  
8 ration was somewhat different, and I wonder if you can  
9 describe a little bit more about that. In the  
10 catheterized population there are actually fewer ACS  
11 patients, and can you speculate on why that is, number  
12 one?

13 I guess number two, was this a casual  
14 triponen drawn in patients to define acute coronary  
15 syndrome?

16 Number three, was the use of invasive  
17 coronary angiography different in the two groups? In  
18 other words, does that signal tell me something about  
19 the difference in the groups?

20 DR. HORTON: Right. The first question  
21 was that they were different in the two groups.

22 DR. HIRSCH: They were different.

23 DR. HORTON: My speculation why that is  
24 the case is that after ischemia if you don't need to,  
25 you wouldn't want to be sticking a catheter through

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1 ventricles that could be potentially irritated for  
2 arrhythmias, et cetera. But I think it's a reasonable  
3 finding as we've discussed it with the Steering  
4 Committee, et cetera.

5 It was a clinical diagnosis, and the  
6 reasons how that diagnosis was confirmed were  
7 collected and included. We did collect cardiac  
8 markers on all patients in the trial actually, not  
9 just in the acute coronary syndrome patients.

10 DR. HIRSCH: So was there a pre-hoc  
11 definition of acute coronary syndrome by these --

12 DR. HORTON: No.

13 DR. HIRSCH: -- markers or the gestalt of  
14 the investigator?

15 DR. HORTON: No, it was based on the  
16 investigator's decision.

17 DR. HIRSCH: And then, I guess, was a use  
18 of invasive coronary revascularization different based  
19 on the patients might feel better and act differently  
20 if one group had had LAD angioplasty and the other  
21 group had not?

22 In other words, were these patients that  
23 came fresh out of my cath. lab into the study?

24 DR. HORTON: Well, these patients, the  
25 first thing, you know, first and foremost was that

1 they had to have dyspnea at rest, and then if they  
2 also had an acute coronary syndrome, then they could  
3 be enrolled in the trial.

4 You know, when you look at the study  
5 procedures that show the investigators decided which  
6 of those patients would be appropriate, we did not  
7 actually collect how many of them when to the cath.  
8 lab. We have some information on the use of some of  
9 the other agents that were used, but not procedures.

10 DR. HIRSCH: Can I'd ask one other follow-  
11 up question on the wonderful double dummy technique?  
12 It's very hard to explain these things, and I  
13 appreciate, again, your ability to try to answer so  
14 many questions in a single definitive study.

15 But, again, the question of blinding  
16 because it's hard to explain the technique and have  
17 everyone follow you no matter how well you try to  
18 explain it.

19 If I were the investigator and my patient  
20 were having the two infusion bags, following up on  
21 Jim's question, clearly if I have a nitroglycerine bag  
22 that I can adjust to any dose I want whenever I want,  
23 since I'm an activist cardiologist today, I'm very  
24 likely if the wedge pressure is high and the patient  
25 dyspneic to really make some manipulations to make

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1 that patient feel better.

2 And if I don't see any change, of course,  
3 in that patient's symptoms or their wedge pressure, I  
4 just unmask that this is actually placebo, maybe. Am  
5 I wrong or right?

6 DR. HORTON: Maybe.

7 (Laughter.)

8 DR. HIRSCH: Because blinding, the  
9 maintenance of blind is essential to understanding the  
10 role of an active drug.

11 DR. HORTON: There are responders and non-  
12 responders, and there's two active agents and --

13 DR. HIRSCH: Okay. I understand.

14 CHAIRMAN PACKER: Okay. We'll just go  
15 right down. So Ileana, Mike if you have any question,  
16 and Marv.

17 DR. PINA: When you were talking about the  
18 catheterized versus the non-catheterized patients, I  
19 got the sense that the catheterized patients somehow  
20 were sicker, more low ejection fractions, et cetera.  
21 But yet the acute coronary syndromes fell on the other  
22 side.

23 There were quite a group of patients who  
24 were concomitantly on dobutamine and dopamine, and  
25 there were a significant number of patients on non-IV

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1 nitrates, and there seemed to be more patients on non-  
2 IV nitrates in the non-catheterized group, which is  
3 where the acute coronary syndrome sits.

4 Do you have any idea of the doses of  
5 nitrates that those patients were on and the doses of  
6 dobutamine and dopamine? Because, I mean, these are  
7 very active agents and may have been started by the  
8 investigator.

9 DR. HORTON: Right.

10 DR. PINA: Obviously, as you said, to make  
11 the patient feel better and continued them.

12 DR. HORTON: Right. Yeah, the short  
13 answer is, no, we did collect that information, but we  
14 didn't summarize that for today.

15 DR. PINA: For either one, for the  
16 dobutamine/dopamine or the nitrates?

17 DR. HORTON: For either, correct. I mean,  
18 I can give you a ballpark if you like. I mean  
19 dobutamine tended to be administered in a five or less  
20 microgram per kilo per minute range, but --

21 DR. PINA: So they were relatively low  
22 dose.

23 DR. HORTON: -- nitrates -- pardon me?

24 DR. PINA: Low dose relatively?

25 DR. HORTON: Yes. There's a range, of

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1 course, but approximately that dose.

2 DR. PINA: And so you say that the dose of  
3 the non-IV nitrates, you don't have that information?

4 DR. HORTON: No, and that's a combination  
5 of isosorbite, you know, the topical nitrates,  
6 sublingual. So it could be done, but we did not  
7 summarize that for today.

8 DR. PINA: Following up, again, on the  
9 double dummy, there seems to be a volume of infusion  
10 that's going to be additive. Let's say that somebody  
11 is on placebo, and the investigator is looking at the  
12 nitroglycerine placebo, up-titrating, up-titrating.  
13 Was that taken into consideration when we look at the  
14 total IV infusion of volume that the patients got?

15 DR. HORTON: Yes, it was. We concentrated  
16 the nitroglycerine preparation so that it's actually  
17 doubly concentrated. So there were 400 micrograms per  
18 milliliter in the bag, and this was an important  
19 training step in case, you know, people were used to  
20 administering nitroglycerine at a certain volume  
21 rather than at a specific dose.

22 And when we looked at the total intake  
23 over 24 hours between Natreacor and nitroglycerine,  
24 they were equal. There were no significant  
25 differences.

1                   But two points to that. We wanted to  
2 prepare both drugs because there were two infusions  
3 going so that the total volume would still be  
4 appropriate for an acute heart failure population, and  
5 then with the anticipation of how the doses would be  
6 infused, that there would be no differences.

7                   DR. PINA: I know that this sounds like  
8 inordinately difficult to get to the right volume.  
9 During that same time, prior to their ability to make  
10 any adjustments, I would imagine, again, the  
11 investigators make the patient feel better, may be  
12 using diuretics, as well, since you allowed diuretics,  
13 and I've seen the mean doses.

14                   How much of that diuretic was given, or  
15 will we hear that from Jim, how much diuretic was  
16 given early on, even prior to your ability to up-  
17 titrate the Natrecor, say?

18                   DR. HORTON: Right. You will hear of that  
19 from Jim. I'll just let him cover that.

20                   CHAIRMAN PACKER: Mike, any questions?  
21 No?

22                   Marv.

23                   DR. KONSTAM: First of all, I just want to  
24 congratulate you on the protocol because I think it  
25 was obviously very thoughtfully responsive to all of

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1 the issues that the FDA had raised before.

2 I also wanted to just make a comment in  
3 response to the question that Ralph was asking about  
4 what to do with the nitroglycerine comparator, and I  
5 just want to comment that in terms -- my response to  
6 that is that the last time around at least one of my  
7 concerns was that we had adverse events, and it was  
8 very hard to really put those adverse effects in a  
9 context of, well, okay, but how good is the drug  
10 compared to some other comparator in terms of, you  
11 know, balancing benefits and harms.

12 So I think from that perspective, I'm glad  
13 you did that.

14 My questions, first of all, you know, so  
15 you stratified by cath. or no cath., and it turned out  
16 that you had almost identical numbers in both. So how  
17 did that happen? Did one complete early and then you  
18 kept going and the other, or what happened there?

19 DR. HORTON: That's correct. The non-  
20 cath. arm completed earlier, and we closed down  
21 randomization, and then completed the study in  
22 catheterized patients. And I think that reflects the  
23 fact that most patients are not managed with the right  
24 heart catheter.

25 DR. KONSTAM: Okay. So there was a point

1 in the conduct of study at which in order for an  
2 investigator to enroll the patient, they had to put in  
3 a catheter, correct?

4 DR. HORTON: Yes, there was a time in the  
5 study that was --

6 DR. KONSTAM: Okay.

7 DR. HORTON: And enrollments slowed down  
8 significantly.

9 DR. KONSTAM: Okay. The thing about that,  
10 getting back to the nitroglycerine comparator, and I  
11 know you've tried to answer this a little bit, I mean,  
12 but if the goal was to try to look for the relative  
13 efficacy of these two agents, the philosophy of the  
14 protocol design seems to me to be a little weak in  
15 this regard because you obviously carefully modeled  
16 what dose you had to achieve based on your experience  
17 with nesiritide to get the hemodynamic effect that you  
18 wanted.

19 Of course, you didn't do anything like  
20 that with nitroglycerine. So my frank reaction to  
21 that is, I mean, it was set up in a way that  
22 nesiritide was going to beat nitroglycerine.

23 Can you comment on that?

24 DR. HORTON: Yes. The goal of the study  
25 was not to compare efficacy of Natrecor to

1 nitroglycerine. This was an added active arm for the  
2 purpose of safety.

3 We will show you efficacy information, but  
4 clearly --

5 DR. KONSTAM: Okay.

6 DR. HORTON: -- the primary endpoint was  
7 versus placebo plus standard care for efficacy.

8 DR. KONSTAM: Okay. So notwithstanding my  
9 earlier comments about why I'm glad you did that arm,  
10 you're concluding that you really cannot -- are you  
11 saying that you really will never be able to really  
12 comment about the relative efficacy of these two  
13 agents if used optimally, whatever that means?

14 DR. HORTON: No. I'm saying that when  
15 nitroglycerine is administered as it is administered  
16 in the real world, which is what happened in VMAC, and  
17 that maybe is something that can be discussed, but  
18 that this is what we have in this study, and that's  
19 how you can view Natreacor versus nitroglycerine.

20 DR. KONSTAM: Okay.

21 CHAIRMAN PACKER: Marv, let me just ask  
22 you to elaborate on that. I get a sense from the  
23 questions of others that there is concern about the  
24 nitroglycerine dosing regimen, and the sponsor made a  
25 choice to let the investigator determine what the

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1 doses were.

2 DR. KONSTAM: Right.

3 CHAIRMAN PACKER: They did not specify in  
4 any of their primary analyses that there would be a  
5 comparison of nesiritide and nitroglycerine, but  
6 obviously those comparisons will be done, and we'll  
7 see those comparisons and those data.

8 The question that arises is if you think  
9 that nitroglycerine is inadequate, is inadequate, is  
10 that you could imagine that it is sufficiently  
11 adequate to act as another placebo. If that's the  
12 case, then comparisons of nesiritide and  
13 nitroglycerine wouldn't be without any interest.  
14 There would be interest.

15 DR. KONSTAM: Oh, yeah. I'm very  
16 interested.

17 No, I agree with what you're saying. I'm  
18 just -- and I'm not sure that this is pertinent to our  
19 deliberations, except to say that I just want to make  
20 clear that, I mean, I'm gathering from what you're  
21 saying -- and this is my inference -- that at the end  
22 of the day you're really not going to be able to say,  
23 "Look. Nesiritide is in some way a better drug than  
24 nitroglycerine."

25 CHAIRMAN PACKER: To my knowledge, I just

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1 want to make sure we keep things focused.

2 DR. KONSTAM: Yeah.

3 DR. D'AGOSTINO: That was -- I'm sorry for  
4 interrupting -- I mean, that was what I was obviously  
5 getting at. I mean, how much do we focus on that for  
6 efficacy and the impression is not at all. And then  
7 the question becomes what about safety and how real is  
8 it as a drug.

9 CHAIRMAN PACKER: Let's try to keep this  
10 focused. To my knowledge, the sponsor is not asking  
11 for a claim vis-a-vis nitroglycerine, correct?

12 DR. HORTON: Correct.

13 CHAIRMAN PACKER: Consequently, you can  
14 look at the nitroglycerine data all you want. There  
15 is no request being made for a claim against  
16 nitroglycerine. Therefore, there is no response the  
17 Committee needs to provide. You get the data, and you  
18 look at it.

19 DR. KONSTAM: I understand. That's why I  
20 prefaced it by saying I'm not sure the remark is  
21 pertinent, but I felt like making it anyway.

22 Okay. And just the last thing. Again,  
23 back to the issue of the analysis of the dyspnea score  
24 and the catheterized versus non-catheterized. So I  
25 just want to understand what the planned -- make sure

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1 I understand what the planned approach to that was  
2 going to be.

3 You know, there obviously was, you know,  
4 knowledge of a concern about this in setting up the  
5 protocol, and yet the plan was to combine them. Well,  
6 what was the plan in terms of determining the  
7 consistency?

8 Was there a stated plan in terms of  
9 analyzing the consistency of effect in terms of the  
10 dyspnea score between the catheterized and non-  
11 catheterized patients? What was your approach to  
12 that?

13 DR. HORTON: The approach was that the  
14 primary analysis was going to include all patients,  
15 and again, the most important reason why that seemed  
16 to be appropriate -- and Dr. Lipicky can speak for  
17 himself, but to us it seemed appropriate -- was that  
18 these agents were being added to standard care, and  
19 everyone knows that even in the short term, patients  
20 get better with IV diuretics even if their wedge  
21 pressure is not reduced.

22 And the other very important point, which  
23 if you ever talk to any of the VMAC investigators, is  
24 that over and over and over again was emphasized that  
25 one of the primary endpoints was dyspnea. This was

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1 not to be discussed with the patient.

2 And I might add that --

3 DR. KONSTAM: Okay.

4 DR. HORTON: -- two years ago -- can I --  
5 sorry.

6 DR. KONSTAM: Well, I think we all  
7 understand that.

8 DR. HORTON: Yeah.

9 DR. KONSTAM: But still, I mean, I'm not  
10 trying to be hard on you on this. Maybe we'll be hard  
11 on you later, okay? I don't know, but I just want to  
12 understand just what your analytic approach was going  
13 to be.

14 DR. HORTON: Well, we --

15 DR. LIPICKY: There wasn't any.

16 DR. KONSTAM: Right.

17 DR. LIPICKY: Okay? I mean, I think  
18 you've elicited that.

19 DR. KONSTAM: Okay. Thanks.

20 DR. HORTON: Actually, the one thing I  
21 will add is that we did use a stratified analysis.

22 DR. D'AGOSTINO: But you responded to me  
23 that you did a two-way analysis, and you looked at the  
24 interaction.

25 DR. HORTON: Yes, and we also looked at

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1 the interaction with the actual data.

2 DR. LIPICKY: But there was no plan for if  
3 there was a difference between the groups what to do.  
4 The primary endpoint was the primary endpoint, and  
5 there was no pre-specified way of dealing with if the  
6 results are a little bit different in the two groups,  
7 and absolutely no plan for how to deal with it if the  
8 results were a lot different between the two groups.

9 CHAIRMAN PACKER: Okay. Bob, you wanted  
10 to ask a question or no?

11 DR. TEMPLE: Well, only to mention what I  
12 think people said before, which was that the  
13 relatively low dose of nitroglycerine used makes for  
14 a sterner comparison as far as safety goes, and that  
15 was the main -- that was probably the main reason to  
16 have the nitroglycerine.

17 CHAIRMAN PACKER: Can I just clarify?  
18 There are other questions on Committee, but I just  
19 wanted to clarify just a few points.

20 The patients were cath.'ed, had a right  
21 heart catheter, and at the time informed consent was  
22 obtained or was the catheter put in after consent was  
23 obtained?

24 DR. HORTON: Either way. It could have  
25 been either way. If the patients had a catheter,

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1 there might have been ongoing dobutamine and were  
2 still dyspneic at rest. It could have been entered  
3 into the trial.

4 During that screening period they'd still  
5 have to meet the hemodynamic criteria.

6 CHAIRMAN PACKER: Okay. I understand.  
7 And how many patients were enrolled in the  
8 catheterization arm after the patients in the non-  
9 cath. arm had stopped enrollment?

10 DR. HORTON: I can get that number for  
11 you. I don't have it on the top of my head.

12 CHAIRMAN PACKER: Let me see if I -- now,  
13 do we know how many people would have been  
14 catheterized and didn't meet the wedge pressure or  
15 whatever other criteria you had, and didn't get the  
16 drug? It's not the same as the screening log concept,  
17 although it seems to be related.

18 The question is: how many people, if they  
19 had a catheter in place, after consent was obtained,  
20 how many people got the catheter, found that the wedge  
21 pressure was less than 20, and didn't get randomized?

22 DR. HORTON: Oh, after. So they didn't  
23 have -- you're asking the question of they didn't have  
24 the catheter. They got consented. They catheterized  
25 them.

1 CHAIRMAN PACKER: Right, because clearly  
2 one would think that if they had the catheter before  
3 consent and the wedge pressure was less than 20, they  
4 wouldn't have been consented.

5 DR. HORTON: Right.

6 CHAIRMAN PACKER: Right.

7 DR. HORTON: There were very few of those.  
8 I believe there were three or four. I discussed them  
9 in great detail with the investigator.

10 CHAIRMAN PACKER: Okay. How many patients  
11 were getting during the -- either at the time or  
12 randomization or any other time; let's say in the  
13 first three hours -- how many were actually getting IV  
14 dobutamine or dopamine, an IV drug for heart failure  
15 other than a diuretic? Because I don't recall seeing  
16 that.

17 DR. HORTON: Right. I will show you that.

18 CHAIRMAN PACKER: And while we're getting  
19 the slide --

20 DR. HORTON: It's in Dr. Young's  
21 presentation. So I can -- would you like me to call  
22 it up now or do you want to --

23 CHAIRMAN PACKER: We can hold on that if  
24 it's part of Dr. Young's presentation.

25 DR. HORTON: Yes.

1 CHAIRMAN PACKER: We can hold.

2 DR. HORTON: Great.

3 CHAIRMAN PACKER: I just want to see if I  
4 got this right. The FDA review makes the point that  
5 in order to get into the study, the patients had  
6 dyspnea at rest or on minimal exertion. I just want  
7 to make sure that I totally understand. Were you able  
8 to document that the patients actually had dyspnea at  
9 rest at baseline at the time of randomization?

10 DR. HORTON: Right.

11 CHAIRMAN PACKER: Because the review  
12 suggests the possibility that some patients may have  
13 entered the study through a somewhat more or less  
14 symptomatic pathway and may not have been dyspneic at  
15 rest at the time of randomization. Do you have any  
16 clarification of that?

17 DR. HORTON: Yes. There were three --  
18 remember that this question was asked of patients. So  
19 usually doctors are the ones who are used to answering  
20 this type of terminology. So we tried to help out the  
21 patients by explaining to them what this might be.

22 And there were actually three levels of at  
23 rest. There was at rest while sitting, at rest while  
24 supine, and at rest with minimal activities, such as  
25 talking, eating, or grooming, not walking.

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1           The next one was shortness of breath with  
2 walking short distances, and then the next one was  
3 shortness of breath with walking greater than 50 feet,  
4 and then the next one was no difficulty breathing.

5           So we talked about that. I think it's up  
6 to your judgment what you think. We thought, and this  
7 was actually a really important training point to the  
8 investigators, that patients who were -- it's more of  
9 a question of what the subject's perception of whether  
10 they have breathing difficulty is, but if they felt  
11 that they were sitting there and felt their normal way  
12 that they feel, which is not great, but they don't  
13 identify it as dyspnea at rest, that the dyspnea with  
14 talking would stimulate them to realize that they were  
15 dyspneic at rest.

16           But I believe that there were only an  
17 additional 18 or 19 percent of the patients that fell  
18 in that category. The 80 percent or more actually had  
19 dyspnea at rest while sitting or supine.

20           CHAIRMAN PACKER: Okay.

21           DR. HORTON: If that helps.

22           CHAIRMAN PACKER: There was no  
23 instructions to the investigators to keep medications  
24 constant in the first three hours?

25           DR. HORTON: No.

1 CHAIRMAN PACKER: Were there any  
2 medications that couldn't be given for a certain  
3 number of hours prior to the start of the infusions?

4 DR. HORTON: No. Well, with the exception  
5 of if the patient was on IV nitroglycerine and they  
6 could withhold it, then it had to be withheld for 30  
7 minutes. Okay?

8 But if they were a catheterized patient,  
9 they needed to be able to assess the patient without  
10 that.

11 And then IV Milrinone and nitrates were  
12 not permitted. So --

13 CHAIRMAN PACKER: How many patients were  
14 getting IV nitroglycerine, let's say, within two hours  
15 of the start of the infusions?

16 DR. HORTON: Very, very few, if any. I  
17 don't recall any, but I will get that answer for you.

18 CHAIRMAN PACKER: Okay. How many times  
19 was wedge pressure measured before the three-hour  
20 wedge pressure measurement?

21 DR. HORTON: How many times was wedge  
22 pressure measured?

23 CHAIRMAN PACKER: Measured.

24 DR. HORTON: At 15 minutes, 30 minutes,  
25 one, two, and three hours.

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1 CHAIRMAN PACKER: Okay. So then an  
2 investigator would know what the wedge pressure  
3 response was before the three-hour assessment, the  
4 earlier wedge pressure response?

5 DR. HORTON: Yes, the investigator would.

6 CHAIRMAN PACKER: Everyone has asked the  
7 question about the double dummy design, and I guess I  
8 won't be an exception to that rule. When you do a  
9 double dummy trial, I guess the easiest way of doing  
10 that would be to make sure that whatever you do with  
11 one dummy you do with the other dummy.

12 Here, this is more complicated than that.  
13 The two dummies weren't the same, weren't handled  
14 exactly the same.

15 DR. HORTON: It is unique.

16 CHAIRMAN PACKER: Yeah. If an  
17 investigator decided that -- the investigator could  
18 adjust the nitroglycerine infusion at will within the  
19 first three hours?

20 DR. HORTON: Yes.

21 CHAIRMAN PACKER: So if the investigator  
22 had a target, a sort of strategy of how to use  
23 nitroglycerine, they could follow that strategy  
24 regardless of when the assessments were made?

25 DR. HORTON: Yes.

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1 CHAIRMAN PACKER: Okay, and that would be  
2 true after the infusions as well at any time? I'm  
3 sorry. After the three hours.

4 DR. HORTON: Yes, yes.

5 CHAIRMAN PACKER: That could be done  
6 anytime. Okay.

7 Why don't we go through the line again.  
8 Yeah.

9 DR. LINDENFELD: Just to clarify what you  
10 asked, I think there's a bigger list of medications  
11 that were withheld two hours before and during the  
12 placebo infusion. At least in our briefing book it's  
13 Milrinone, unblinded, nitroglycerine, dobutamine,  
14 nitroprusside, IV ACE inhibitors.

15 DR. HORTON: No, not dobutamine or  
16 dopamine.

17 DR. LINDENFELD: Okay. New infusion, any  
18 new infusion?

19 DR. HORTON: A new infusion. I'm sorry.

20 DR. LINDENFELD: The ACE inhibitors.

21 DR. HORTON: The question was could you  
22 have a dose change in the first -- right.

23 DR. LINDENFELD: No, didn't you ask  
24 what --

25 DR. HORTON: Let me clarify that.

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1 CHAIRMAN PACKER: It was two separate  
2 questions. One is could you be receiving; second,  
3 could there be a dose change.

4 DR. HORTON: Right. Okay. For  
5 dobutamine/dopamine, because it was permitted that  
6 study drug could be added to dobutamine or dopamine,  
7 what we wanted them to do was to make sure that  
8 patients had dyspnea at rest while receiving  
9 dobutamine or dopamine. So we asked them to receive  
10 a stable dose of dobutamine or dopamine for the two  
11 hours to assess their dyspnea at rest after being on  
12 a stable dose for two hours.

13 After study drug was started, there was no  
14 restriction. They could have continued to go off on  
15 dobutamine.

16 DR. LINDENFELD: Well, that's not what our  
17 briefing booklet says. What it says is that they had  
18 to be -- this may be incorrect, but it says they had  
19 to be held constant through the three hours of placebo  
20 controlled period.

21 DR. HORTON: Sorry. They were deemed a  
22 treatment failure if they went up. In other words, if  
23 they had to go up on the dose to urgently -- you're  
24 right that there is some confusion. I apologize for  
25 that, but it did say that they should keep the dose of

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1 dobutamine or dopamine stable for the first three  
2 hours. I misspoke earlier, but if they had to for  
3 patient safety, then they could do that, and it was  
4 deemed a treatment failure.

5 That means in the analysis we measured the  
6 endpoint of treatment failures and there were very  
7 few.

8 CHAIRMAN PACKER: How did you incorporate  
9 that into your primary analysis, or you didn't?

10 DR. HORTON: We didn't because there were  
11 only two patients.

12 CHAIRMAN PACKER: I see.

13 DR. HORTON: But we didn't have a pre-  
14 specified plan for doing that either.

15 CHAIRMAN PACKER: Let me just ask one more  
16 question. You suggested you designed the study so  
17 that the ability to adjust nesiritide was an option  
18 only in the patients having a catheter.

19 DR. HORTON: Correct.

20 CHAIRMAN PACKER: Because your  
21 instructions to investigators was that a wedge  
22 pressure was their primary reason for adjustment.

23 DR. HORTON: And the blood pressure.

24 CHAIRMAN PACKER: And the blood pressures  
25 are a limiting factor.

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1 DR. HORTON: Right.

2 CHAIRMAN PACKER: Why didn't you allow the  
3 adjustments to be made in the non-catheterized  
4 patients? They could have adjusted the infusion based  
5 on symptoms.

6 DR. HORTON: Right. We just simply didn't  
7 do that because the study was already -- you know, had  
8 enough elements in it that we didn't really want to  
9 complicate it anymore. So we wanted to provide a  
10 prescription in a few patients so that we could  
11 collect some safety information.

12 CHAIRMAN PACKER: Would the implications  
13 be that you could only adjust the medication if you  
14 had a catheter in?

15 DR. HORTON: Well, in the VMAC trial that  
16 was true.

17 CHAIRMAN PACKER: Would you think that  
18 that would be a general concept?

19 DR. HORTON: It's a very good question.  
20 It does down to the total database, and we have over  
21 200 patients that actually received the .015 and the  
22 .03 doses who were not catheterized, and those were --  
23 the safety in those studies represent the worst case  
24 scenario in a sense because the doses were actually  
25 started at those doses.

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1                   So what VMAC provides is patients who were  
2 started at .01, tolerated it and went up, and you  
3 know, we didn't think of it as a critical issue for  
4 whether a catheter might be required or not, given the  
5 fact that none of the other agents that are out there  
6 required right heart catheter, and they're actually  
7 titratable agents.

8                   So we figured that would be a discussion  
9 we could later have.

10                  CHAIRMAN PACKER: Okay. Why don't we go  
11 down the Committee again? I'm sorry, Ralph. You had  
12 any additional questions?

13                  DR. D'AGOSTINO: No. I'm anxious to hear  
14 the next presentation.

15                  (Laughter.)

16                  CHAIRMAN PACKER: We all are.

17                  Steve.

18                  DR. NISSEN: I'm also anxious to hear the  
19 next presentation. I wanted to give you a heads up  
20 about something I'm looking for data-wise that I know  
21 you're not necessarily the one to provide, but maybe  
22 you can pull this together while Jim Young is up  
23 there.

24                  I want to know in those patients in whom  
25 the bag, the nitroglycerine bag, contained placebo

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1 what the dose of nitroglycerine would have been had  
2 that been nitroglycerine, if you follow what I'm  
3 saying, because I want to know what happened. How  
4 much did the investigators go up on those placebos?  
5 It gives me a much better sense of what they were  
6 doing there with the nitroglycerine.

7 CHAIRMAN PACKER: Does anyone have any  
8 other urgent comments before proceeding?

9 Okay. Jeff.

10 DR. BORER: This isn't a comment. It's  
11 really a question about what you're going to present.  
12 When I read the submission, I assumed that you were  
13 doing what you said you were doing, which was adding  
14 the nitroglycerine arm to get a sense of safety with  
15 another vasodilator, and I thought in the booklet you  
16 submitted to us you presented an appropriate  
17 evaluation, that is, how much blood pressure down for  
18 how much wedge pressure down. Are you going to talk  
19 about that some time later so that we'll get into that  
20 again or are you going to --

21 DR. HORTON: Yes, there will some of that  
22 information presented in both efficacy and safety.

23 DR. NISSEN: Thank you.

24 DR. HIRSCH: I'll try to be brief. Dr.  
25 Packer mentioned that we were here in '99 and today

1 we're trying to again review a new set of data for  
2 this which includes the new outcome variable, which is  
3 symptom change for an acute heart failure drug, and I  
4 find that to be interesting and, to use a pun,  
5 precedent setting.

6 So the question comes --

7 CHAIRMAN PACKER: It's not precedent  
8 setting. It was -- I know, but it's not precedent  
9 setting. It was part of the original development  
10 program. It was suggested by the division in its  
11 discussions with the sponsor. It was a point of  
12 significant discussion in the January 1999 meeting.  
13 so it is not new.

14 DR. HIRSCH: I'll reframe my question, Mr.  
15 Chairman.

16 (Laughter.)

17 DR. HORTON: It's new as a primary  
18 endpoint.

19 DR. HIRSCH: Right. So the question then  
20 comes in study design before we look at data. It's  
21 hard to look at quality of life data or dyspnea data,  
22 and I believe that this is a new scale. So let's talk  
23 about the scale before we look at the data.

24 Challenging question I realize, but is  
25 there a pre-specified level of clinical significance

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1 that the investigators and the Steering Committee  
2 would have thought was important before one does the  
3 analysis for a p value for a change in dyspnea?

4 DR. HORTON: No, there wasn't a pre-  
5 specified discussion about that.

6 DR. HIRSCH: As expected, it's hard to do  
7 that, but nevertheless it's clinically relevant.  
8 We'll be talking about that later, I'm sure.

9 And then sort of the same question. You  
10 mentioned looking at significance for both outcomes,  
11 one of which is the symptom change. How does one  
12 power trial for a change in a dyspnea scale when there  
13 is no previous use and no standardized range of  
14 sensitivity to a known intervention?

15 DR. HORTON: It was very difficult to do.  
16 We gave it our best shot. We estimated what the  
17 distribution of the responses would be in placebo plus  
18 standard care, assuming that many of them would be  
19 improved, and then we just powered for additional  
20 effects with Natrecor.

21 And the other part of the total sample  
22 size was on the safety end, that, you know, we wanted  
23 to substantially add to the safety database, but it  
24 turns out that the sample size was really primarily  
25 driven by the efficacy endpoint because of the

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1           subjectivity --

2                   DR. HIRSCH: Which efficacy endpoint?

3                   DR. HORTON: -- of the response -- sorry?

4                   DR. HIRSCH: Which efficacy endpoint?

5                   DR. HORTON: The dyspnea evaluation, yes,  
6           definitely.       The study is overpowered for  
7           hemodynamics.

8                   DR. HIRSCH: Is there more that one can do  
9           other than guess at what power one would need or what  
10          sample size one would need to achieve power? Is it  
11          really just a guesstimate?

12                   DR. HORTON: Well, you know, the study  
13          that we had previously was 325. So we used that as a  
14          baseline, and then we modified what we thought the  
15          responses would be because now this was added to  
16          standard care, and how to guess exactly how many  
17          patients were receiving IV diuretics and dobutamine or  
18          whatever would be improved at three hours was  
19          difficult.

20                   CHAIRMAN PACKER: But that one, it's  
21          always a guess.

22                   DR. HIRSCH: I understand. Thank you.

23                   CHAIRMAN PACKER: Ileana, and then, Ray,  
24          you have the last word.

25                   DR. PINA: Just a couple of very brief

1 things. I see how you did the pharmacodynamic  
2 modeling to come up to a new bolus that had not been  
3 used in 311, -25 or -26 --

4 DR. HORTON: Right.

5 DR. PINA: -- and a much lower infusion  
6 rate.

7 DR. HORTON: Right.

8 DR. PINA: How did you come up with the  
9 up-titration where you gave another bolus and then you  
10 took it up to the lowest dose that you had used in the  
11 other three trials?

12 DR. HORTON: Right. What we wanted to do  
13 with the modeling was to compare. We did use modeling  
14 to actually select the dosing regimen, and again,  
15 there were two parts of that which was what the bolus  
16 would be, and then what the incremental increase would  
17 be.

18 And the goal of that primarily was to  
19 compare it to the lowest infusion dose that was  
20 previously studied so that we would end up with a  
21 dosing regimen that had a better safety profile than  
22 the lowest infusion dose, and we studied several bolus  
23 doses, for example, and we studied changes every three  
24 hours, every six hours, every two hours, and this was  
25 the regimen that basically predicated that the safety

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1 profile would be better than what was observed with  
2 the .015.

3 DR. PINA: And you took that all with the  
4 modeling?

5 DR. HORTON: Yes.

6 DR. PINA: With pharmacokinetic modeling.

7 DR. HORTON: Yes.

8 DR. PINA: In the previous IND, we had  
9 brought up questions about hemo concentration,  
10 increase in protein albumin. All of this had been  
11 talked about before. Did you collect hematologic  
12 data? Did you collect serum albumin protein?

13 Because I saw you collecting creatinine.

14 DR. HORTON: Right.

15 DR. PINA: I guess that was the other  
16 question. Did you collect the other values and will  
17 we see those?

18 DR. HORTON: No, creatinine was the only  
19 laboratory value that we collected.

20 CHAIRMAN PACKER: Okay. Ray.

21 DR. LIPICKY: Just to anticipate a  
22 discussion that will come, the guideline for symptoms  
23 is different from placebo, period, without the  
24 stipulation that it has to be different by some  
25 amount. And I imagine we'll talk about that some.

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1 CHAIRMAN PACKER: Well, I think as a  
2 general concept, this Committee and, I think, the  
3 division has not known what magnitude of effect one  
4 should deem clinically significant. The only data  
5 that I can -- the only discussions I can remember  
6 where the magnitude was important was, one, when there  
7 was a risk and one had to do a risk and benefit  
8 weighing, or the other time is when the magnitude of  
9 the effect is on a surrogate, and one doesn't know how  
10 large an effect on the surrogate one needs to have  
11 because one doesn't necessarily know what the  
12 surrogate means.

13 And the typical example of that would be  
14 the treatment of hypertension, what drop in  
15 millimeters of mercury is, quote, clinically  
16 important.

17 Other than that, we generally have said  
18 that anything that, quote, beats a comparator is  
19 interpretable, and then you can weigh risk to benefit.

20 Is that approximately right?

21 DR. LIPICKY: Yep.

22 CHAIRMAN PACKER: Bob?

23 DR. TEMPLE: It's not that you couldn't  
24 think of other ways to do it, but in many settings,  
25 it's so hard to show anything at all, even for the

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1 drugs we all believe work, that setting new null  
2 hypotheses at, you know, at least ten percent, at  
3 least 15 percent is hard to support. We noticed that  
4 in depression and other places. It's pretty hard to  
5 even beat placebo, even for the drugs we're pretty  
6 sure work.

7 CHAIRMAN PACKER: Okay. Why don't we move  
8 forward?

9 And while the next speaker is coming up,  
10 I just want to emphasize how useful it was to this  
11 Committee to have a presentation on design before one  
12 sees a presentation of results. We don't get that  
13 opportunity very often, and maybe you took that  
14 opportunity because the design had some special need  
15 for discussion, but I think in general it is very  
16 useful to have a presentation on design because it  
17 really allows us to focus on what was -- on the  
18 discussions and though processes that occur before the  
19 trial started, something which is very useful in  
20 interpreting the results of the study.

21 So to distinguish a presentation on study  
22 design from a presentation on study results is always  
23 helpful. So this was particularly helpful.

24 DR. YOUNG: Chairman Packer, members of  
25 the Committee, Dr. Lipicky, Dr. Temple, VMAC is the

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