

1 the use of nesiritide when compared with placebo?

2 Now, this is not the same because this is
3 together with earlier studies.

4 DR. PINA: This is together, I think,
5 primarily with --

6 DR. LIPICKY: Together with .325.

7 DR. PINA: With 325, right.

8 CHAIRMAN PACKER: Right.

9 DR. PINA: So I would have to say, yes,
10 placebo.

11 CHAIRMAN PACKER: You have the same
12 choices. You can say yes, no or sort of, I guess.

13 DR. PINA: I say yes.

14 CHAIRMAN PACKER: So Ileana says yes, and
15 Ralph we'll start with you on this one.

16 DR. D'AGOSTINO: Yes.

17 DR. NISSEN: Yes.

18 DR. LINDENFELD: Yes.

19 DR. BORER: Yes.

20 DR. GRABOYS: Yes.

21 DR. HIRSCH: Yes.

22 DR. ARTMAN: Yes.

23 DR. KONSTAM: Yes.

24 CHAIRMAN PACKER: Sort of.

25 Next question. The same question, was

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1 there a symptomatic benefit associated with use of
2 nesiritide when compared with nitroglycerine?

3 DR. PINA: Well, that would only have to
4 be VMAC because that --

5 CHAIRMAN PACKER: That's right. That's
6 the only thing we've got.

7 DR. PINA: -- where the comparison was
8 made, and I would have to say no.

9 CHAIRMAN PACKER: You would say no. Okay,
10 and Marv.

11 DR. KONSTAM: No.

12 DR. ARTMAN: No.

13 DR. HIRSCH: No.

14 DR. GRABOYS: No.

15 DR. BORER: No. I just want to qualify
16 this to say that within the context of the study that
17 was done, we learned something about the drug, but,
18 no, I can't say that it's better than nitroglycerine.

19 DR. LINDENFELD: No.

20 DR. NISSEN: No.

21 DR. D'AGOSTINO: No. I mean --

22 DR. LIPICKY: That 24-hour symptom then --

23 CHAIRMAN PACKER: I was just going to --
24 I haven't voted.

25 DR. D'AGOSTINO: Well, are you talking

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1 about the three -- are we shifting from the three-hour
2 to the 24-hour?

3 CHAIRMAN PACKER: It doesn't matter. It's
4 a question. My --

5 DR. D'AGOSTINO: Well, there's the quality
6 -- well, there was the overall quality and so forth
7 that was asked as the end, which is different. I'm
8 taking this to be the three hour.

9 CHAIRMAN PACKER: This is at three or 24
10 hours. It has to be.

11 DR. LIPICKY: It was intended for 24
12 hours, but in fact, it could be three, six, or 24
13 because you're looking at all of the studies, and
14 you've already answered the placebo question.

15 CHAIRMAN PACKER: All right. Would anyone
16 change their vote based on the fact that the intent
17 here was 24 hours?

18 Ralph, you would?

19 DR. D'AGOSTINO: I'd move it more to the
20 sort of, but it's certainly evidenced with the 24
21 hours, but I have to defer in some sense to the dosage
22 problem with the nitroglycerine.

23 CHAIRMAN PACKER: Yeah, I have to say that
24 -- and I am clearly in a minority here -- I found the
25 comparison with nitroglycerine at 24 hours very

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1 reassuring because I am not remotely concerned about
2 the fact that the dosing with nitroglycerine was
3 inadequate. I don't think there's a whole lot of
4 disagreement.

5 But even if I thought the nitroglycerine
6 was placebo, the fact that nesiritide beat
7 nitroglycerine at 24 hours in spite of the fact that
8 the dose of nitroglycerine was revved up, and in spite
9 of the fact -- and I'm particularly reassured by that
10 because the unblinding issues that caused many people
11 to say sort of or some people to say sort of don't
12 exist at 24 hours. In fact, the effect was more
13 marked in the non-catheterized patients than in the
14 catheterized patients.

15 And to me, there's no way you can do that
16 unless you have a drug that is -- I'm not saying
17 there's a claim against nitroglycerine. I'm not
18 saying that the sponsor is asking for one or if they
19 ask for one that it should be granted, but I actually
20 found the data vis-a-vis nitroglycerine to be
21 extremely helpful in interpreting the data vis-a-vis
22 placebo.

23 DR. LIPICKY: Right, and I need to add to
24 what Milton said in that this is not a comparative
25 claim. It is does nesiritide give you symptoms

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1 relief, and you can treat nitroglycerine as placebo or
2 as something that works, but it's not better than
3 nitroglycerine at the right dose and everything else.

4 DR. BORER: Okay. So you're just
5 specifically asking do you believe the comparison that
6 was made in VMAC. Is that the question?

7 DR. LIPICKY: Yes.

8 DR. BORER: Because if it is, then I have
9 to change my vote to yes.

10 DR. LIPICKY: Yes, yes. I thought you --

11 DR. BORER: Yes, I believe the comparison
12 that was made in VMAC.

13 CHAIRMAN PACKER: Okay. Ralph.

14 DR. D'AGOSTINO: Maybe I'm not pulling out
15 the right chart and so forth, but I thought the
16 overall comparison wasn't significant, that it was
17 only in the subset where it was significant.

18 CHAIRMAN PACKER: I agree. The effect on
19 dyspnea was a p value of .1. The effect on the global
20 score was .075. And although those do not reach
21 nominal levels, 24 hours, .044?

22 DR. D'AGOSTINO: Well, there's a .126
23 that's no significant differences --

24 CHAIRMAN PACKER: Right, okay.

25 DR. D'AGOSTINO: -- were observed between

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1 the treatment set and the whole study population.

2 However, within the non-catheterized
3 stratum, there was significance.

4 CHAIRMAN PACKER: Okay. I don't think we
5 need to dwell on this. Let me ask a question. I
6 don't think it matters whether this Committee think
7 that the comparison of nitroglycerine is supportive or
8 persuasive. I think you get a sense from this
9 Committee that the dosing of nitroglycerine makes
10 comparative claims against nitroglycerine impossible,
11 but the use of an active comparator here maybe viewed
12 by some people in the committee and perhaps many of
13 the people in the Committee as useful not only in
14 terms of the safety, but also in terms of efficacy.

15 Is that fair?

16 DR. LIPICKY: Yeah, it's fine.

17 CHAIRMAN PACKER: Along with hemodynamics
18 is demonstration that an agent reduces the symptoms of
19 heart failure -- now, let me emphasize this is
20 hemodynamics and symptoms together -- sufficient for
21 its approval for decompensated heart failure.

22 There's no safety component to this
23 question. The question that is being asked is if you
24 had a drug that improves hemodynamics and improves
25 symptoms, would that be sufficient to satisfy the

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1 efficacy requirements of a short-term treatment for IV
2 heart failure or do you need more data. Do you need
3 data on morbidity and mortality? Do you need other
4 things?

5 Because we say we need other things
6 perhaps for other conditions. So the question that
7 arises is if you had symptoms, if you had
8 hemodynamics, would that be sufficient from the
9 efficacy --

10 DR. KONSTAM: Could I understand? Because
11 I'm not sure I agree with what you just said. In
12 terms of efficacy, I don't think we or the FDA has
13 ever said that if you improve symptoms that that's not
14 sufficient to show efficacy, let's say, in chronic
15 heart failure.

16 CHAIRMAN PACKER: That's not the question.

17 DR. KONSTAM: But that's what you just
18 said.

19 DR. LIPICKY: No.

20 CHAIRMAN PACKER: No.

21 DR. KONSTAM: You said sometimes for other
22 things we require other things besides symptoms.

23 CHAIRMAN PACKER: Oh, yeah, but that
24 wasn't referring to chronic heart failure.

25 DR. LIPICKY: Well, maybe the way to --

1 let's change the wording a little bit. Up above it
2 was asked is pulmonary capillary wedge pressure
3 enough, not sufficient; is it enough, and basically
4 some people thought so and some people did not.

5 So now the question is you have pulmonary
6 wedge pressure, and you have something else, like
7 symptoms. Is that enough? That's to get at the
8 people who said pulmonary capillary wedge pressure
9 isn't enough.

10 It may be that some of the people that
11 said pulmonary capillary wedge pressure isn't enough
12 wouldn't be satisfied with that and symptoms. That's
13 what this has elicited. That was what that was --
14 that is what this was meant to elicit, if that
15 makes --

16 DR. KONSTAM: Can I just ask a question?
17 Is there a condition -- I mean, just because Milton
18 brought it up, is there a condition in which
19 demonstration of symptom improvement that's clear cut
20 is not sufficient to accept an efficacy indication?

21 DR. LIPICKY: No, you're 100 percent
22 right. We would certainly say that that was okay, but
23 now this is assuming no risk, right?

24 DR. KONSTAM: Right, assuming no risk.

25 DR. LIPICKY: And if there is a risk side,

1 then you may need more there.

2 DR. KONSTAM: No, assuming no risk.

3 DR. LIPICKY: But this is assuming no
4 obvious risk. We don't want to get too complicated
5 yet.

6 DR. BORER: You know, i don't want to
7 prolong this discussion because I think we're
8 meandering here, but we don't approve anti-anginal
9 drugs unless they also show an anti-ischemic effect.
10 I think that's the parallel here.

11 You're asking if you have symptoms and you
12 have a plausible basis for the reduction in symptoms,
13 and it's not just the --

14 DR. LIPICKY: Well, that's fine.

15 DR. BORER: Is that combination good
16 enough? And the answer is yes or no.

17 DR. LIPICKY: That's right.

18 CHAIRMAN PACKER: Okay. I think what's
19 being asked of us here -- actually I'm not certain
20 what's being asked of us here. Can we skip this
21 question?

22 DR. LIPICKY: Yes.

23 CHAIRMAN PACKER: Okay.

24 (Laughter.)

25 CHAIRMAN PACKER: Consider Hypotension.

1 How did the incidence duration and severity of
2 hypotension associated with nesiritide compare with
3 placebo or nitroglycerine?

4 We'll cover both of those. Ileana.

5 DR. PINA: Okay. Now, this is VMAC,
6 right?

7 CHAIRMAN PACKER: This is the totality of
8 the data.

9 DR. PINA: This is the totality of the
10 data.

11 DR. LIPICKY: Everything you know.

12 DR. PINA: Pardon?

13 DR. LIPICKY: Everything you know.

14 DR. PINA: Okay. The incidence, duration,
15 and severity of hypotension with nesiritide is much
16 higher and worse than placebo. In the doses that were
17 used in VMAC, it is comparable to nitroglycerine in
18 severity, but not in duration, and actually not even
19 in incidence. There's still a higher number of
20 hypotension episodes with the nesiritide drug.

21 And so the second question has to be with
22 VMAC because you don't have another comparison trial.

23 CHAIRMAN PACKER: Modifications of what
24 Ileana said?

25 Let's just make sure. The comparison here

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1 to placebo seems self-evident. So the only question
2 is the comparison to nitroglycerine.

3 Jeff?

4 DR. BORER: Maybe we can just pull out the
5 data and look. My recollection is that the incidence
6 and severity were similar with nitroglycerine. It was
7 just the duration that was different. Am I --

8 DR. PINA: No, I said the severity was the
9 same.

10 DR. BORER: Yeah, the severity was the
11 same, but also the incidence is the same.

12 DR. PINA: If I'm not mistaken, there were
13 a few more cases in the Natreacor group than in the
14 nitroglycerine group of hypotension, maybe not
15 symptomatic hypotension, but if you look at your data
16 of blood pressures below 80, there were more in the
17 Natreacor group.

18 Maybe I misread that slide.

19 CHAIRMAN PACKER: Dr. Horton, would you
20 like to just clarify? Just come up to the microphone
21 because we need it for the record.

22 DR. HORTON: The incidence of symptomatic
23 hypotension was five percent with nitroglycerine and
24 four percent with Natreacor overall. When you asked
25 for the number of patients whose lowest blood pressure

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1 fell below 80 at any time during the first 24 hours,
2 there were 13 percent of nitroglycerine patients and
3 14 percent Natrecor patients. That was not
4 necessarily associated with --

5 DR. PINA: It's not a significant -- well,
6 the question doesn't say symptomatic hypotension. It
7 just says hypotension, and with placebo, obviously I'm
8 going with the totality of the data.

9 So I would say that, you know, based on
10 the percentage that you just gave me, the incidence is
11 very similar, but the duration is much longer.

12 CHAIRMAN PACKER: Okay. So the difference
13 here vis-a-vis nitroglycerine is duration. Does
14 anyone disagree with Ileana's --

15 DR. PINA: And we need to qualify the
16 doses that were used in VMAC, which is very different.

17 CHAIRMAN PACKER: Okay. And does anyone
18 want to modify anything that Ileana has said in
19 summary?

20 Okay. Let's keep going. The
21 complications associated with hypotension. Increases
22 in creatinine or acute renal failure, similar with
23 nesiritide and nitroglycerine.

24 Let me modify this question because it is
25 possible that the increases in serum creatinine are

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1 not associated with hypotension. So let's change the
2 question and say we're -- was the frequency or
3 severity or duration or however you want to say it of
4 increases in serum creatinine or acute renal failure
5 similar with nesiritide or nitroglycerine.

6 DR. PINA: I would have to say no. I
7 would have to say they were different primarily
8 because of the duration of the hypotensive episode,
9 and I believe, Alan, that you were pointing out at
10 least two patients who ended up with dialysis.

11 So I think they're similar, but certainly
12 not identical.

13 CHAIRMAN PACKER: I'm sorry. Can you
14 clarify that again? You just referred to Alan's
15 point, but Alan said there was a difference.

16 DR. HIRSCH: Well, just to clarify for all
17 of us, I think the global data set, we weren't
18 presented with evidence that there is a global
19 difference in the total data set. I pointed out --
20 right? Correct?

21 PARTICIPANT: Right.

22 DR. HIRSCH: But I did notice a blip that
23 concerned me both in the global data set as well as in
24 the acute population.

25 DR. PINA: But in the global data set, we

1 don't have nitroglycerine. We only have
2 nitroglycerine and VMAC. So I think that the duration
3 of the hypotensive episodes with the drug concerns me.

4 CHAIRMAN PACKER: That's not the question.
5 The question, we have changed the question. It has
6 nothing to do with hypotension anymore. It's a
7 straightforward question. Is either the frequency or
8 severity of increases in creatinine similar with
9 nesiritide and nitroglycerine?

10 That's the question, because the way the
11 question is framed now it would only enable us to
12 answer the question if it was related to hypotension.
13 We have previously established in the course of the
14 discussion that there may or may not be a relationship
15 to hypotension.

16 So the question should be straightforward,
17 and the reason is there is no other place in the
18 discussion where we can discuss this. So we need to
19 discuss this now.

20 So the question is: is the frequency or
21 severity of increases in serum creatinine or renal
22 dysfunction or however you want to frame it, similar
23 with nesiritide and nitroglycerine?

24 DR. PINA: If I look at the FDA data that
25 has been supplied to us, looking at number with

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1 creatinine increases of more than .5, there were more
2 patients in the Natrekor fixed dose group that had
3 come from placebo and then had been randomized
4 compared to the other groups.

5 So, no, I can't say they're the same.

6 CHAIRMAN PACKER: You know, I need to
7 clarify one other thing. This is not just based on
8 VMAC. This is based on the totality of the data
9 because it doesn't say just VMAC. It's the whole NDA.

10 So it's not just VMAC. It's all the
11 studies, and your answer may differ depending on which
12 study or which dose or however you want to define it.

13 DR. PINA: You're not comparing it to
14 nitroglycerine then anymore.

15 CHAIRMAN PACKER: No, we're just saying --

16 DR. PINA: You're just saying general.

17 CHAIRMAN PACKER: Un-huh.

18 DR. PINA: But you have nitroglycerine in
19 there.

20 DR. LIPICKY: Nitroglycerine was not
21 mentioned in the original words. This is --

22 CHAIRMAN PACKER: This says
23 nitroglycerine.

24 DR. HIRSCH: The question I want to ask:
25 is there a demonstrable effect of --

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1 CHAIRMAN PACKER: Oh, I see. You don't
2 want that answer, right, or you do want that answer?

3 DR. LIPICKY: Well, you can't the way it's
4 structured. So forget it, or do you want to write two
5 new questions?

6 CHAIRMAN PACKER: We don't have to write
7 two new questions. The first question is: is there
8 a -- let's just put it this way. Is there a concern
9 about increases in serum creatinine or the severity of
10 increases? Is there a concern about increases in
11 serum creatinine with this drug compared with placebo,
12 first, and then compared with nitroglycerine second?

13 DR. LIPICKY: Right.

14 CHAIRMAN PACKER: Very straightforward.

15 DR. PINA: The first answer is yes.

16 CHAIRMAN PACKER: Okay.

17 DR. PINA: And the second answer is still
18 yes because even in the nitroglycerine group there are
19 more patients by percent who have an increase in
20 creatinine of greater than .5 in the Natrecor group,
21 and that's according to the FDA documentation that
22 we've been given.

23 DR. LIPICKY: Do you recall the numbers?

24 DR. PINA: Well, I have them right here,
25 and this is --

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1 DR. KONSTAM: What page are you on?

2 DR. PINA: This is on page 68 of the VMAC
3 analysis. There's a table there, Table 48, and it
4 talks about the summary of the renal effects, and the
5 agency looked very carefully at patients who had
6 baseline creatinines of two or treater and divided it
7 up into those who had an increase of greater than .5,
8 and there I don't know what the statistical
9 significance of those numbers are, but they are
10 different. Thirty-two percent --

11 DR. LIPICKY: Can't you say what the
12 numbers are?

13 DR. PINA: Thirty-two percent in the
14 Natrecor fixed group that had been on placebo and then
15 been randomized and 28 percent on the nitroglycerine,
16 the patients working on placebo and then randomized to
17 nitroglycerine.

18 DR. KONSTAM: See, Ileana, that's just one
19 cell. I mean if you look at the other --

20 DR. PINA: I understand that.

21 DR. KONSTAM: -- Natrecor cells, it's not
22 really there.

23 DR. PINA: I understand that, but it is
24 mentioned.

25 DR. KONSTAM: Right. The right-hand

1 corner.

2 DR. PINA: Right, and if you look at all
3 of them, the nitroglycerine group had 21 percent, and
4 the Natreacor fixed dose had 28 percent of increases
5 over .5.

6 CHAIRMAN PACKER: Okay. Can we have some
7 discussion on this? Ileana's answers are, yes, there
8 is a concern that exists with respect to placebo or
9 nitroglycerine. Any other discussion?

10 Jeff.

11 DR. BORER: Yeah, I think that I have a
12 concern similar to Ileana's, but I have to enter -- I
13 have to note that my concern is related in part to
14 dose, and inferences based on very few data at the
15 higher doses.

16 I have less of a concern about the .01
17 infusion dose, more of a concern as you go up.

18 Certainly I can't place a quantitative
19 value on my concern because the data are too few, but
20 I have the sense that something may be going on here,
21 and I'd like to be reassured that it is not, and I
22 can't be reassured from the data as they exist now.

23 CHAIRMAN PACKER: Okay. Let's have some
24 more discussion. Steve.

25 DR. NISSEN: Well, I think statistically

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1 speaking it's hard to make a case that there's
2 anything in the renal function data. The problem is
3 that there's enough there, and the numbers being
4 relatively small, this is not an adverse endpoint that
5 occurs very frequently.

6 And so to get a statistical answer, we
7 would need to have a much, much larger experience with
8 the drug. And so if the question is statistically
9 based, you know, I don't think there's compelling
10 evidence statistically that there is a worse outcome.

11 Am I worried about it? Yes, I am worried
12 about it.

13 DR. PINA: I don't think the question was
14 made on a statistical basis. It was just meant to ask
15 was there a concern, and we're asked to put in the
16 totality of the data, and there was a concern in 325
17 and 326.

18 And to me the concern is still here in
19 VMAC, and I agree with Jeff that this is probably dose
20 related because the doses here were much smaller, and
21 the fact that more patients came in with a higher
22 creatinine sine this was more reality.

23 CHAIRMAN PACKER: Okay. I'll ask you to
24 clarify in a second. How many of you think that this
25 concern which -- forget about statistical issues

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1 because the number of events is too small to allow
2 calculation of a meaning p value.

3 How much of your concern would be
4 alleviated if the dose was limited to .01 micrograms
5 per kilogram per minute. In other words, how much of
6 your concern is drive by the events at higher doses?

7 DR. PINA: Well, I think it would be
8 considerably drive by the events at higher doses.

9 CHAIRMAN PACKER: Alan?

10 DR. HIRSCH: A good deal, half of it, my
11 concern would be diminished if we kept at the .01
12 dose, but I do believe, again, the data set there is
13 even smaller so that there is still residual concern
14 that requires more data collection, concomitant data
15 collections, et cetera.

16 CHAIRMAN PACKER: Steve, Joann, Jeff,
17 anyone else? Anyone want to comment on this?

18 DR. KONSTAM: Yeah, I mean, I agree with
19 that. I think that the numbers, you know, at the .01
20 dose in this study do not concern me in and of
21 themselves, and I think it's the fact that we saw some
22 at the higher doses that sort of substantiates that.

23 So I share the point. It's not a big
24 concern to me at .01 dose.

25 DR. NISSEN: Milt, I just want to add the

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1 caveat that the fact that there were two patients that
2 went to dialysis who were acute coronary syndrome
3 patients makes me worry a little bit more that
4 contrast dye -- I mean, we know that there's a lot of
5 interaction between contrast and other agents in
6 producing acute renal insufficiency, and if this drug
7 were to get out into general use, you know, this is a
8 potentially important concern.

9 If it somehow potentiated the nephrotoxic
10 effects of contrast, that would be potentially a
11 signal there in those two dialysis cases among the
12 acute coronary syndrome patients who probably got
13 cathed.

14 CHAIRMAN PACKER: Jeff.

15 DR. BORER: To put this in an operational
16 context, if we decided at the end of the day to
17 suggest to the FDA that this drug is approvable at
18 this time, then I would want to mandate obtaining more
19 data about this particular issue.

20 Certainly if we didn't think it was
21 approvable, I think they'd be getting more information
22 about this issue somehow, and I don't want to start
23 designing studies in the vote on a question here.

24 But I think we're all concerned that there
25 aren't enough data to allow us to give optimal

1. instructions for use. So we want to be very
2 conservative and get some more information.

3 CHAIRMAN PACKER: Okay. Yes, please, and
4 identify yourself.

5 DR. SHRINER: I'm Dr. George Shriner, and
6 I'm the Chief Scientific Officer at Scios, but I'm
7 commenting also in the context of my being a
8 nephrologist.

9 And I just wanted to make one comment
10 about the data that was used in the table that was not
11 a part of the Scios definition of renal failure. And
12 addition of .5 milligrams per deciliter of creatinine
13 superimposed on a cutoff of two is a very different
14 proportional decrease in the amount of filtration than
15 going from one to 1.5 or from 1.5 to two. It is a 25
16 percent decrease in GFR, and this is superimposed on
17 a patient population where the admission creatinines,
18 instead of being excluded as they often are in these
19 studies, went from one to 11.

20 So one is talking about a very small
21 change even looking at the percentages, and creatinine
22 GFR superimposed on a population that has considerable
23 preexisting renal insufficiency.

24 CHAIRMAN PACKER: Was the definition you
25 used to define renal insufficiency -- how was that

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1 obtained?

2 DR. SHRINER: It was obtained as a
3 functional definition of closer to a 50 percent
4 decline in GFR of a .5 -- it was less than two. I
5 believe it was 1.5. It was a 50 percent decrease to
6 a value greater than two, not starting at two and
7 going to .5.

8 CHAIRMAN PACKER: I know, but that was
9 protocol specified?

10 DR. SHRINER: Yes.

11 CHAIRMAN PACKER: That was in the original
12 protocol? It's an arbitrary definition?

13 DR. SHRINER: But it was prospectively
14 defined.

15 CHAIRMAN PACKER: No, wait. It's an
16 arbitrary definition? It was not in the protocol, and
17 you're complaining about the FDA's arbitrary
18 definition?

19 DR. SHRINER: No, I'm not complaining.
20 I'm just pointing out that a change of .5 milligrams
21 per deciliter when you start with a population of two
22 has a different significance than when you go from one
23 to 1.5. That's all.

24 DR. LINDENFELD: But it might not have had
25 a different clinical significance. I mean, that's

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1 still a pretty big jump acutely to go from two to 2.5.

2 DR. PINA: The 11 patient, the patient
3 with 11 is a way far outlier in the patient
4 creatinine. Below that is six and a half, 5.3, and
5 there's like three or four patients. Everybody else
6 crowds around two, two and a half, which is closer to
7 the mean.

8 DR. LIPICKY: That's okay. We hear your
9 concern, and I think that's noted. So we're okay
10 there.

11 CHAIRMAN PACKER: Okay. Consider
12 morbidity. I'm going to skip Question 3.3 because I'm
13 not certain -- oh, no. Actually 3.3, was the
14 incidence of hypotension or other adverse events
15 related to hypotension different from earlier studies?
16 I think the answer is yes, and it was probably related
17 to the lower dose. I think the answer is yes, and I'm
18 not certain that there's a lot of issues related to
19 that; is that correct?

20 DR. PINA: I agree.

21 CHAIRMAN PACKER: Okay. Consider
22 morbidity, Question No. 4. How important is it that
23 a sponsor provide long-term information on morbidity,
24 that is, hospitalization, for drugs developed as
25 treatment for acute heart failure?

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1 Do you think that sponsors should do this?

2 DR. PINA: To me the answer is yes because
3 we have all seen drugs that acutely do something good,
4 and then when the drug is stopped there is either
5 rebound or we see the ill effects of the drug later.
6 So I think collecting that information is very, very
7 critical.

8 CHAIRMAN PACKER: Does anyone disagree?

9 Okay. If it is important, what amount of
10 -- and since we're going to collect the data and
11 they're going to do a treatment comparison, and they
12 are not going to power the trial to detect the
13 difference. This is a very important statement. No
14 sponsor is going to power a study to detect a
15 difference in morbidity. They'll want to assume that
16 there is either a favorable effect or a neutral
17 effect.

18 And the major concern we have is that it
19 not be adverse. So the question is: how much adverse
20 do they need to exclude in designing their trials?
21 How much data do they have to collect?

22 With what degree of confidence do they and
23 we and the division need to know that, in fact, an
24 excess morbidity hospitalization has been excluded?

25 And in your answer to that, think for a

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1 moment how one defines this. Does one define this as
2 a recurrent hospitalization? Does one define this as
3 the duration of the initial hospitalization?

4 Because these could lend themselves to
5 very different answers, and is this a clarification or
6 a vote?

7 We'll start with Ileana. Ileana.

8 DR. PINA: Well, I think that in chronic
9 heart failure, since a lot of the morbidity comes from
10 the repeated hospitalizations, then I would think that
11 the repeated hospitalizations would be a very
12 significant component of morbidity.

13 Length of stay, as well, and particularly
14 if the hospitalization is for recurrent or worsening
15 heart failure, and again, it's the same symptoms that
16 brought the patient in for the first time. Can I give
17 you a percentage?

18 No. First of all, I'm not statistician.
19 So I can't give you a percentage, but we know what the
20 data are for the average heart failure patient who has
21 X number of admissions, and the highest recurrence and
22 readmission rate occurs in the first 90 days.

23 So I would like to see no excess
24 rehospitalizations at least in those first 90 days to
25 give me some sense of comfort, and to me that would be

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1 a very important factor by --

2 CHAIRMAN PACKER: What do you mean by no
3 excess? Like is one percent too much? Is three
4 percent too much? Should the sponsor calculate a
5 relative risk and have a confidence interval on the
6 right side, which is less than something?

7 DR. PINA: I think I would like to see the
8 relative risk of a population that's similar to this
9 in their readmission rate, and see it go at least not
10 to the wrong side of that, of what an average
11 population with heart failure at this age.

12 CHAIRMAN PACKER: If there's a neutral
13 effect, there's a 50 percent chance it will go to the
14 wrong side.

15 DR. PINA: If there were a neutral effect,
16 I would feel some comfort.

17 CHAIRMAN PACKER: No, no. How do you
18 define neutrality?

19 DR. PINA: I'm not sure how to define
20 neutrality in this.

21 CHAIRMAN PACKER: Okay.

22 DR. LIPICKY: With no effect.

23 DR. PINA: With all honest.

24 CHAIRMAN PACKER: Well, no effect, but
25 it's a point estimate with confidence intervals. The

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1 presumption here is that, similar to the question on
2 mortality, that the agency has provided casual
3 guidance to sponsors that somehow you need to make
4 sure your drug doesn't do a lot of harm.

5 Numbers have been proposed as to what that
6 right sided confidence interval should be. I think
7 isn't this what the question is about, Ray?

8 DR. LIPICKY: Yeah. Well, it's a little
9 more complicated than what you're proposing, I guess.
10 The question sort of is if the two treatments have
11 absolutely the identical effect on rehospitalizations,
12 half of the time the point estimate of one is going to
13 be above the other, and half of the time the point
14 estimate of the other is going to be above the other,
15 and that's with no effect.

16 So are you interested in just point
17 estimates and their confidence limits, and you just
18 look at them and say, "I like that," or are you
19 interested in more precision for those point estimates
20 so that you can actually make a statement from them?

21 And then the question would be what upper
22 bound would you like to have the confidence limit of
23 the new agent exclude. Like here what Scios says is
24 they can exclude a 20 percent excess with their 95
25 percent confidence bounds for mortality. Would that

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1 be the same rule for morbidity, that is,
2 rehospitalizations, or would you want to see ten
3 percent or is 100 percent okay?

4 CHAIRMAN PACKER: Ray it may or may not
5 affect the way we answer this question to know what
6 you would do with this information.

7 DR. LIPICKY: Well, we're asking you. We
8 don't have that requirement now.

9 CHAIRMAN PACKER: Well, I guess there are
10 a couple of things you could do with our answer. You
11 could ask sponsors to meet that requirement, and if
12 they don't meet it, then they don't get approved.

13 DR. LIPICKY: Right.

14 CHAIRMAN PACKER: Or you could say to
15 sponsors that the Committee recommended this, and if
16 they exceed the boundary that we talk about, that it
17 would appear in labeling, but it would not be an
18 approvability issue.

19 DR. LIPICKY: Oh, well, but I guess what
20 we're asking here is your sense of what that should
21 be. Okay. I am -- for example, let me just be the
22 devil's advocate for the moment. I'd be willing to
23 approve it on the basis of pulmonary capillary wedge
24 pressure, and I'd accept a 100 percent increase in
25 rehospitalizations.

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1 Okay. You might think I'm a nut. So
2 we're asking you what is it that you think the right
3 numbers here are, and we recognize that this is not
4 anything precise, and that it's likely to change and
5 that with more thought it is likely to change, but
6 it's sort of to get a sense of what you're thinking.

7 You're not answering a definitive question
8 forever.

9 CHAIRMAN PACKER: Okay. That's not even
10 the question. The question is: do you want us to
11 answer this based on frequency of rehospitalization or
12 the duration of the index hospitalization?

13 DR. LIPICKY: Well, that's your choice.
14 What you saw in this data is that the duration of
15 hospitalization was increased, and then for 90 days
16 most hospitalizations are within 90 days
17 rehospitalizations. Well, if that's reasonable, I
18 would feel very funny telling somebody to add that 90-
19 day data with absolute certainty because I can't
20 conceive of how 24 hours of treatment with something
21 that doesn't affect the heart directly, that is, it's
22 not affecting the myocardial cells or some
23 regenerative process or remodeling or something like
24 that, can likely be expected to alter the natural
25 history of heart failure.

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1 But you are saying to us at this instant
2 in time on the basis of what Ileana said, that you
3 want some assurance that there's no rebound, quote,
4 unquote.

5 CHAIRMAN PACKER: It's not just rebound.
6 You could easily imagine, and some of us fear that,
7 for example, a drug like dobutamine can have even
8 during a short-term infusion effects which are very
9 long lasting because it may kill cells. One doesn't
10 know until one asks.

11 DR. LIPICKY: Well, it could.

12 CHAIRMAN PACKER: Yes, and
13 theoretically --

14 DR. LIPICKY: The question is -- let me
15 put it this way. If you had not made that assertion,
16 I would not have dreamed of it in my wildest dreams
17 that that was possible. So what we're asking is:
18 what are your wildest dreams? What do we want to say?
19 What are we concerned with here? And what kind of
20 long-term data is required?

21 DR. HIRSCH: So as a proposition, how
22 about keeping it very simple and not putting a greater
23 burden on sponsors? I don't know that we're ready to
24 answer that definitively. How about simply length of
25 stay as the sponsor has done, rehospitalization

1 numbers, and net six-month hospitals days? Don't put
2 any limits around it, and in a year we'll come back
3 and readdress it.

4 DR. LIPICKY: That's fine. So you might
5 vote on that, Milton, and see if everybody thinks
6 those are two reasonable things.

7 CHAIRMAN PACKER: Well, let's ask for just
8 a little discussion first. Steve and Jeff and who
9 else?

10 DR. NISSEN: I actually think it's a
11 really important and relevant question because I
12 suspect, as I suspect Milton does, that some of the
13 drugs that we currently use for acute congestive heart
14 failure do, in fact, adversely affect short-term
15 outcome, that is, morbidity and so on, and so I would
16 be fairly rigorous here, and I might set a standard of
17 not being somewhere in the range of ten or 20 percent
18 worse than those point estimates. I don't want them
19 to be more than ten or 20 percent on the wrong side
20 because I think that we're in this particular
21 therapeutic class.

22 DR. LIPICKY: No, you don't want to say
23 what --

24 CHAIRMAN PACKER: Yeah, he really doesn't.

25 DR. LIPICKY: That's not a very wise

1 statement.

2 DR. KONSTAM: Steve, that's going to
3 require an enormous population

4 DR. LIPICKY: The rest of what you're
5 saying I understand, but what you explicitly said is
6 not a good thing to say because it doesn't account for
7 the confidence limits, and you're just talking about
8 point estimates, and you don't want to --

9 DR. NISSEN: Okay, yeah. Right, okay.

10 DR. KONSTAM: Can I pick a number? How
11 about if we pick a number? I'll say 30 percent for
12 hospitalizations.

13 DR. LIPICKY: Excess, rule out.

14 DR. KONSTAM: Yeah, rule out excess.

15 DR. LIPICKY: Ninety-five percent
16 confidence.

17 DR. KONSTAM: Yeah.

18 CHAIRMAN PACKER: Wait, wait. What
19 variable of hospitalization are you talking about, 30
20 percent?

21 DR. KONSTAM: Combined hospitalization and
22 mortality, hospitalization for heart failure or death.

23 CHAIRMAN PACKER: Time to event? Index
24 hospitalization matter? I mean if you say 30 percent,
25 you have to refer to something.

1 DR. KONSTAM: Time to event.

2 CHAIRMAN PACKER: Time to first
3 rehospitalization. Index hospitalization doesn't
4 matter, right?

5 DR. KONSTAM: Time to rehospitalization
6 for heart failure or death.

7 CHAIRMAN PACKER: Time to
8 rehospitalization for heart failure or death, 30
9 percent. That's very specific.

10 DR. LIPICKY: Okay.

11 DR. BORER: Okay. I'd like to suggest
12 that we have no basis for creating standards, numbers
13 or anything else. You know, as far as I'm concerned,
14 the morbidity has to be understood relative to the
15 benefit, and that requires a series of qualitative
16 judgments.

17 I think it's important that the sponsor
18 should describe what happens to the patient. The
19 determination of the relationship between benefit and
20 risk is something that's a result of a lengthy and
21 detailed Talmudic discussion like we're having now,
22 and I think that we ought to not try to answer this in
23 a specific way.

24 The sponsor ought to describe what
25 happens. You know, off line at another time perhaps

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1 we can determine all of the parameters that might be
2 described, or maybe the sponsor can determine what it
3 thinks is important to describe, but I wouldn't go any
4 further than that.

5 DR. D'AGOSTINO: What are we talking about
6 in terms of morbidity compared to what? I mean, back
7 to the clinical trial or, I mean, what's the
8 comparison? Whatever the randomized groups were, we
9 want them to be -- I mean, I think I agree that we
10 don't know what we're talking about, but I think also
11 that we can say something.

12 I would pick a period of time, something
13 like a follow-up of three months and the 30 percent
14 and so forth. You can find tune that as you go along,
15 but it sort of gives the direction that we're talking
16 about some period of time we should be paying very
17 close attention to these individuals in follow-up,
18 keeping track of hospitalizations and mortality, and
19 I would combine hospitalizations and mortality as the
20 endpoint and talk about the excess in comparison with
21 the other drug.

22 DR. LIPICKY: I understand what everybody
23 is saying, and maybe we should cut this short, but so
24 okay. I'm real clever in how I design, recruit, and
25 so on and so forth, and I get my six-month follow-up,

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1 and what I bring are -- and I'll just put it in events
2 -- what I bring are a total of 30 events for this
3 length of hospitalization. Okay? And you know you're
4 not going to be able to draw any conclusions from
5 that, but I followed your guidelines, and now, Jeff,
6 you'll be able to look at this and say something.

7 And is that the environment you want to
8 create?

9 DR. BORER: If the alternative is
10 mandating that 10,000 or 20,000 patients with acute
11 exacerbation of heart failure have to be studied in
12 order to make a more precise determination of what the
13 drug is doing that's bad to compare with what it's
14 doing that's good, I would say, yeah, what you just
15 said before I gave the outlandish number is good
16 enough. It's the basis on which we make many
17 decisions.

18 DR. LIPICKY: Okay, but you could sort of
19 say you have to have enough of the size of your trial
20 so that you have enough events that you can tell
21 something in the range of 20 percent difference or
22 something on that order and give some rough guide
23 because then you know whether you're talking hundreds
24 of events, thousands of events or ten events is
25 enough.

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1 DR. BORER: You could, and that's not
2 unreasonable, but I could conceive of a situation in
3 which a drug made somebody feel extraordinarily better
4 when you looked out six months because of a chain of
5 therapy or whatever, but the hospitalization
6 invariably was longer. The index hospitalization
7 invariably was longer, significantly

8 Is that bad, good, indifferent? I don't
9 know. I mean I'd have to look at the data.

10 DR. LIPICKY: Well, given that setting,
11 you would be -- I would imagine I would -- be less
12 interested in the 60-day follow-up and the 30-day
13 follow-up and so on, but you don't know that ahead of
14 time. You've got to start a trial. You're
15 randomizing patients, and if it's only pulmonary
16 capillary wedge pressure, you only have to randomize
17 ten.

18 If you've got to get some other benefit,
19 you might have to randomize a few hundred, and if
20 you've got to get some kind of rehospitalization
21 benefit, you've probably got to randomize more than
22 that, and you've got 1,500 that you probably ought to
23 randomize all told because we haven't got to do you
24 want to know how many big toes fall off and rare
25 things.

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1 So this is really intended to give some
2 feeling, and I think you have. I think you have given
3 us all of the feeling we need and all the feeling that
4 people need at the present time to, you know, sort of
5 evaluate where they are, and they take their risks.
6 If there's not much of an effect, then you're going to
7 be very worried about all of this other stuff.

8 If there's a real big effect, you'll be
9 less worried about all of this other stuff.

10 CHAIRMAN PACKER: Ray, let me propose a
11 different paradigm. It wasn't that long ago, and I'm
12 going back to the early 1990s. Before large scale
13 morbidity, mortality trials in chronic heart therapy
14 were mandated or highly recommended, that one would
15 take a look at the mortality data or morbidity data in
16 a relatively short term or intermediate term placebo
17 controlled trial that focused on exercise tolerance
18 and derive the point estimate with confidence
19 intervals.

20 And that point estimate and confidence
21 intervals was described in labeling. There's actually
22 one example of that.

23 DR. LIPICKY: No, I understand, but
24 remember yesterday. Okay? We had one randomized
25 trial with 24,000 patients over four years, and 381

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1 controlled clinical trials in the drug development
2 database couldn't come anywhere near addressing the
3 problem. So we're in a different era now. Okay?
4 We're starting to think differently, and it's
5 important to recognize that, where the safety database
6 that came from 380 controlled clinical trials didn't
7 come anywhere close to one randomized, 24,000 patient
8 trial that ran for four years.

9 And I think you have to recognize that
10 we're in this changing paradigm again. I don't see
11 any way out of that, and how soon it's going to be
12 necessary to have those kinds of trials I don't know.
13 That's part of what we're talking about now. So I
14 don't think you really have to answer this question
15 because I don't think you know the answer. I don't
16 think we know the answer, and I don't think anyone has
17 thought about it very hard yet.

18 CHAIRMAN PACKER: Well, we promise we'll
19 think about it really hard, and we'll get back to you.

20 DR. LIPICKY: In August.

21 CHAIRMAN PACKER: In August. Does that
22 sound reasonable?

23 DR. LIPICKY: Okay. We should actually
24 have a session on what does safety mean.

25 CHAIRMAN PACKER: Right. Okay. The

1 answers are not necessarily identical for mortality.
2 They're not necessarily identical. We'll go through
3 this quickly.

4 Ileana, how important is it -- well, first
5 of all, let me ask the question. What you really want
6 to know, Ray, is is this committee concerned about the
7 morbidity data with nesiritide. That's the real
8 question.

9 The question that we've been trying to
10 answer is philosophical, but the real question is are
11 we concerned about the morbidity data with nesiritide.

12 Ileana, are you concerned?

13 DR. PINA: I think from the data that I
14 have seen, particularly the readmission rate, no, I'm
15 not concerned.

16 CHAIRMAN PACKER: Okay.

17 DR. PINA: I think we've gotten the
18 information.

19 CHAIRMAN PACKER: Okay. Is anyone
20 concerned about the morbidity data with nesiritide
21 that's been presented?

22 No, no, no. Hospitalization,
23 hospitalization. I'm not talking about renal. I'm
24 not talking about any other definable AE. I'm talking
25 about the hospitalization data because that's how

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1 we're defining morbidity.

2 Anyone concerned?

3 DR. HIRSCH: Not concerned, but I note the
4 one-day length of stay, but overall not concerned.

5 CHAIRMAN PACKER: Okay.

6 DR. LIPICKY: I think that the mortality
7 question can get answered the same way, Milton.

8 CHAIRMAN PACKER: Okay, fine. Let's not
9 talk about the philosophy of mortality. Let's ask the
10 Committee: are you concerned about the mortality data
11 with nesiritide as it has been presented by the
12 sponsor?

13 Ileana, are you concerned?

14 DR. PINA: No.

15 CHAIRMAN PACKER: Is anyone concerned?

16 DR. KONSTAM: Well, I'd just like to
17 comment on it. You know, I think that my reading of
18 the data, you know, I would throw out the PRECEDENT
19 study as I've said because I don't think dobutamine is
20 an appropriate comparator for this, and if you throw
21 it out, you know, I think what we saw was that the
22 upper boundary on mortality endpoint was 40 percent.

23 CHAIRMAN PACKER: If as randomized, it's
24 probably 50 percent.

25 DR. KONSTAM: Okay. so it's 50 percent.

1 Just to define are we worried or not worried, I mean,
2 I'm a little bit worried. I'm a little bit worried.
3 I think, you know, we've got to be a little bit
4 worried if we cannot rule out a mortality effect
5 smaller than a 50 percent increase. So I'm a little
6 bit worried.

7 CHAIRMAN PACKER: Okay. Let's just go
8 through this quickly. We did this before. You're not
9 worried. You're a little worried. You're a lot
10 worried. I don't know how else to do this.

11 Ileana, are you not worried, a little
12 worried, a lot worried?

13 DR. PINA: I'm not worried.

14 CHAIRMAN PACKER: Okay. We'll start
15 with --

16 DR. KONSTAM: I'm a little worried.

17 DR. ARTMAN: I'm not worried.

18 DR. HIRSCH: Not worried.

19 DR. GRABOYS: A little worried.

20 CHAIRMAN PACKER: Tom, please. We --

21 DR. GRABOYS: Not worried, not worried.

22 CHAIRMAN PACKER: All right. Jeff?

23 DR. BORER: I'm a teeny little bit
24 concerned so that I'd like to see data as they come
25 out, but basically not worried.

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1 DR. LINDENFELD: I'm just a little bit
2 worried, just a little bit.

3 DR. NISSEN: I'm a little worried, too.

4 DR. D'AGOSTINO: Not worried.

5 CHAIRMAN PACKER: I'm a little worried.
6 How did we count Jeff's vote?

7 I think you want your vote to count that
8 you're not worried, right? Okay. He's a little
9 worried. Are you a little worried?

10 DR. BORER: I must comment here. I mean
11 we're talking about six-month mortality after a two-
12 day infusion, a one-day infusion. I mean I can't get
13 overly excited about that. I'd like to see more data
14 as they become available perhaps in some way from the
15 experience in the field, but does this reach the level
16 where I want to put a stop to the use of this agent?
17 No, of course not.

18 CHAIRMAN PACKER: That'll come later.

19 DR. HIRSCH: But you don't have long-term
20 experience with this drug class. You can't compare it
21 to other drug classes where we have lots and lots of
22 long-term experience, and the point estimate is harder
23 to feel comfortable with.

24 DR. LIPICKY: I think you've answered our
25 question though.

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1 CHAIRMAN PACKER: Fine, terrific. Is
2 there adequate experience on which to base a
3 description of the safety and efficacy of nesiritide
4 in patients with acute ischemic origin with preserved
5 systolic function or receiving other drugs common in
6 the treatment of decompensated heart failure?

7 Ileana, take all three.

8 DR. PINA: From the acute ischemic origin,
9 I praise the company for including those patients.
10 The numbers are still small. So I don't think that I
11 can make a lot of statements about that.

12 The same with preserved systolic function.
13 I'm very happy that they included them because they
14 are a problem when they present, but again, I think
15 the numbers are small. So I can't make any
16 significant statement to say there's adequate
17 experience. There's one trial.

18 CHAIRMAN PACKER: Let me remind the
19 Committee that the sponsor has proposed a labeling,
20 which is in their briefing document. The labeling
21 proposed by the sponsor specifies that the drug would
22 be indicated in patients with or without acute
23 ischemic syndrome regardless of the cause of heart
24 failure and whether or not they're taking concomitant
25 medication.

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1 So this is really directed towards the
2 proposed labeling that the sponsor has put forth.

3 DR. PINA: I just added up, and there are
4 61 patients which were listed with acute ischemic
5 syndromes in one trial. So I would have to say, no,
6 I can't say there's enough experience, and the same
7 goes with preserved systolic function.

8 Am I comfortable with patients receiving
9 other drugs? Yes. I think that they included all
10 sort of drugs that these patients were on, multiple,
11 and saw no signal necessarily to make us worried.

12 CHAIRMAN PACKER: Okay. So Ileana
13 suggests insufficient data with acute ischemic,
14 insufficient data with preserved systolic function.
15 It's sufficient not to block approvability, but
16 insufficient to get a claim because that's, I think,
17 the question here.

18 DR. KONSTAM: Yeah, but can I? I just
19 want to comment on this because I've wondered about
20 the logic about this, and I think here's the
21 situation.

22 The company has done now what it was told
23 to do, and here we are with really a few patients in
24 these different categories represented, and what do
25 they mean?

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1 I mean, I really don't -- you know, I
2 agree with what Ileana said. I don't think we can
3 say anything broadly about the safety or efficacy, for
4 that matter, but let's focus on the safety in these
5 two populations, preserved ejection fraction and acute
6 coronary syndromes.

7 So I agree with what she said, and the
8 question is what lesson have we learned. I mean I
9 wonder about, you know the advocacy of including these
10 patients because I don't know what the message is that
11 we get.

12 CHAIRMAN PACKER: I think that's a valid
13 point, Marv, but this Committee specifically said to
14 the sponsor and advised the division that we were
15 concerned that they didn't have data.

16 DR. KONSTAM: Right, exactly, and I
17 questioned it at the time, and I'm just saying here we
18 are again, and I don't think we gain anything from it.

19 DR. LIPICKY: And it did not good.

20 DR. KONSTAM: And it did no good. That's
21 the point I'm making.

22 DR. LIPICKY: So I don't disagree with
23 Marvin at all.

24 CHAIRMAN PACKER: Jeff.

25 DR. BORER: I don't think that's

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1 completely fair. I mean, there are some data. Yeah,
2 it hasn't told us all we might want to know about the
3 safety of the drug in these subpopulations, but
4 certainly there was no suggestion that the bottom
5 dropped out in these groups and that, oh, my goods,
6 what's going to happen here?

7 So I think that rather than talk about a
8 claim, one might, you know, step away from that for a
9 moment and suggest that if this drug is approved for
10 use in people with heart failure, perhaps what's known
11 should be described somewhere so that people can be
12 careful.

13 You know, although I don't know what I
14 want to know, I know that most people seem to do okay.

15 DR. KONSTAM: Well, I would take the
16 opposite view, Jeff, because, you know, I think that
17 these two groups, the preserved ejection fraction
18 group and acute coronary syndromes are different from
19 the rest of the population in some very important
20 ways, and if we're saying, you know, we require 500
21 patients in a randomized data set to get comfortable
22 with the safety, well, we're nowhere near that in
23 these special populations.

24 DR. LIPICKY: Okay. Let me change the
25 question then. Okay, Milton? And see if you agree

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1 with changing it this way, and forgetting about what
2 the sponsor wrote in the label.

3 Let's make the question such that should
4 labeling exclude treatment of these kinds of
5 populations, forget about claiming you have
6 something, but should it say do not use in these
7 populations, and maybe that's the way in which you
8 should answer yes or no to these questions.

9 CHAIRMAN PACKER: Okay. the question is:
10 should the labeling preclude or exclude or say do not
11 use this drug in patients with acute ischemic
12 syndromes or preserved systolic function or receiving
13 other drugs common to treatment of decompensated heart
14 failure?

15 DR. KONSTAM: So this is purely the safety
16 side of the question? It has nothing to do with
17 efficacy?

18 DR. LIPICKY: Yes, right. It is should --
19 well, it's both, right? Do you know enough to not say
20 do not use in these populations or the alternative is
21 to be silent.

22 DR. HIRSCH: I think you don't want to
23 either promote nor exclude. I think we have some
24 preliminary data, and we can make recommendations in
25 either direction.

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1 CHAIRMAN PACKER: But, Ray, the original
2 question was whether a positive statement could be
3 made, which is what the sponsor had --

4 DR. LIPICKY: No, that wasn't what the
5 original question was. It was well known that there
6 were only 20 patients and you'd have to say no.

7 CHAIRMAN PACKER: Okay.

8 DR. LIPICKY: So that isn't what the
9 purpose was, but it was should you exclude a
10 population.

11 CHAIRMAN PACKER: So let's vote on that.
12 Should labeling specifically say that patients like
13 this shouldn't receive the drug?

14 Ileana?

15 DR. PINA: You can't say that, no.

16 CHAIRMAN PACKER: Okay. Ralph, we'll
17 begin with you.

18 DR. D'AGOSTINO: No. I mean, I think the
19 study did include these types of individuals. My
20 sense is from the analysis and presentations that
21 there was nothing surprising or upsetting, and in the
22 particular groups, realizing that they do vary, so I
23 think a no is appropriate.

24 DR. NISSEN: I guess I'm very concerned,
25 and the reason I'm concerned is that hypotension,

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1 particularly more prolonged hypotension in people with
2 ischemia can be extremely troublesome and can get you
3 in an awful lot of trouble.

4 And so on a theoretical basis, I would be
5 very uncomfortable with allowing this drug to be given
6 to sick patients.

7 DR. LINDENFELD: I agree with Steve. I'd
8 be very uncomfortable. I think I might exclude acute
9 ischemia on the basis of this or at least suggest that
10 very few patients with acute ischemia have been
11 treated with this drug.

12 CHAIRMAN PACKER: All right. Jeff?

13 DR. BORER: I would vote no. I think that
14 if the drug is approved that the label should describe
15 what's known, but I'd also point out to everybody that
16 if somebody comes in with decompensated heart failure,
17 how are you going to know a systolic function when
18 you start to treat them?

19 CHAIRMAN PACKER: Right, but Steve's
20 suggestion was the acute ischemic syndrome.

21 DR. BORER: I understand. There are two
22 populations here. I'm concerned about both, and I'm
23 agreeing really with Joann that I would want to say
24 what's known, although I wouldn't exclude them.

25 But with regard to the second population,

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1 I'm suggesting that that's a very difficult group to
2 deal with since in the common setting people come in
3 with heart failure and you may not know what their
4 systolic function is before you need to treat them.

5 CHAIRMAN PACKER: Let me make sure that
6 we've got everyone on track. Ralph said he would not
7 exclude any of these three. Steve said that he only
8 one that he would recommend excluding would be acute
9 ischemic. Joann agreed with that, and Jeff, you
10 wouldn't exclude any.

11 Okay. Tom.

12 DR. GRABOYS: I wouldn't either.

13 CHAIRMAN PACKER: Okay. Alan.

14 DR. HIRSCH: Exclude no group, but limited
15 experience in acute ischemia. I have a theoretical
16 worry.

17 CHAIRMAN PACKER: Okay. Ileana.

18 DR. PINA: I would say exactly what Alan
19 was saying. I would not exclude them, but I would
20 make some statement about limited experience.

21 CHAIRMAN PACKER: Okay. Michael.

22 DR. ARTMAN: Yeah, I can live with that.

23 DR. KONSTAM: Okay. You know, I think
24 that patients with acute ischemic syndromes, but also
25 patients with so-called diastolic dysfunction who have

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1 hypertrophic myopathies, hypertrophic hypertensive
2 disease, certainly restrictive myopathies, as one
3 patient sneaked in here with this, the idea of giving
4 an acute potent vasodilator with a very long
5 hemodynamic effect, pharmacodynamic effect to me is a
6 very scary proposition, and this data set does not
7 provide me with enough comfort to say that it's okay
8 to use this drug in those populations.

9 CHAIRMAN PACKER: Okay. I guess my sense
10 is I'm not concerned about acute ischemic origin
11 because I think this drug acts in a manner very
12 similar to nitroglycerine. Although it is longer
13 acting, I guess I'm less concerned than others.

14 I think the sponsor has really done what
15 the division asked them to do in terms of
16 incorporating these patients. It's hard to know what
17 database in patients with acute ischemic origin can be
18 viewed as being sufficient because, I mean, 61
19 patients might sound small, but, gee, is 200 the magic
20 number, 400, five? It's hard to know. It's
21 impossible to know exactly where our comfort level
22 should be.

23 But I agree with Marv's cautionary
24 comments that patients with hypertrophic
25 cardiomyopathy, patients with known restrictive

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1 cardiomyopathies, we don't know what the risk to
2 benefit relationship is in those cases, and I would
3 have concern about that. The labeling should make
4 some statements along those lines.

5 DR. LIPICKY: Skip seven, Milton, because
6 you weren't provided any information at this meeting
7 regarding that question.

8 CHAIRMAN PACKER: Okay. We actually were
9 on the hemodynamics.

10 DR. LIPICKY: Well, very little.

11 CHAIRMAN PACKER: Okay. That's fine.
12 Let's go on to eight. If nesiritide were to be
13 approved for the treatment of decompensated heart
14 failure, what should the labeling say?

15 And let me just make an observation.
16 Frequently we answer this question after we vote for
17 approval, but sometimes it's hard to know how to vote
18 for approval unless you know what you're voting for.
19 So that's the reason why the question has been
20 reversed.

21 So if it were to be approved for the
22 treatment of decompensated heart failure, what should
23 it say about the patient population, the benefits of
24 treatment, dose, duration of treatment, effect on
25 symptoms, effect on mortality, the need for central

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1 monitoring or any special warnings or
2 contraindications.

3 DR. KONSTAM: Milton, before we do that,
4 I just had a thought. To go back to the safety issue
5 for a second, I'm sorry to do this, but I'm thinking
6 again.

7 In terms of patients with low wedge
8 pressures probably in my mind ought not go on this
9 drug. Now, they specifically included patients, of
10 course, who did not have Swan-Ganz catheters in, but
11 I want to sort of propose that the patients who didn't
12 have Swan-Ganz catheters in were inferred to have high
13 wedge pressures, and there was clinical judgment
14 applied and probably investigators did a great job
15 about that and didn't get into trouble, but I believe
16 that you could really get into trouble giving this
17 drug to people who have wedge pressures of eight or
18 ten millimeters of mercury.

19 And so I just want to make that point so
20 that what I'm inferring from the database is that you
21 ought to be pretty confident that you actually have a
22 patient who has an elevated wedge pressure before
23 giving the drug, and if you're not sure, you probably
24 ought to be using the Swan in my judgment.

25 So sorry to go backwards, but we haven't

1 made that point.

2 DR. LIPICKY: Well, that's manageable in
3 labeling, right?

4 DR. KONSTAM: Yeah, I think so.

5 CHAIRMAN PACKER: Okay. Anyone disagree
6 with that?

7 All right. There's eight possibilities
8 here, and I'm going to try and consolidate the eight
9 possibilities, and let me take them in an order which
10 is somewhat different than the order in which they're
11 stated.

12 The first question, I think, probably that
13 we should ask ourselves is what should be the
14 indication for treatment. What are the benefits of
15 treatment?

16 And there are a variety of ways of
17 approaching this. One is to say the drug is indicated
18 for the treatment of or short-term treatment of acute
19 decompensated heart failure, period, no description of
20 what the drug does.

21 Second is it's indicated for the short-
22 term treatment of decompensated heart failure to lower
23 wedge pressure or to improve symptoms or both, or
24 anything else we think might be appropriate.

25 So let's talk about what we think the

1 indication should read. Then what I want to do is
2 talk about the dose and duration of treatment, the
3 patient populations, and any safety issues.

4 Ileana, what should be the wording of the
5 indication for treatment?

6 DR. PINA: I would say that the patient
7 population is acute heart failure with an elevated
8 wedge pressure, whether found by catheter or
9 whether --

10 CHAIRMAN PACKER: That's the population.
11 We're not doing population.

12 DR. PINA: What did you ask first?

13 CHAIRMAN PACKER: Right, just -- no, no.
14 I reframed it. The indications for treatment should
15 either be non-specified; it's just indicated for the
16 management of these patients, and we'll talk about
17 what the patients are, or it's indicated to do
18 something, either lower wedge pressure or improve
19 symptoms or something else.

20 DR. PINA: I would say the patient with an
21 acute presentation of heart failure, and at that
22 statement I would stop. I wouldn't say to lower wedge
23 pressure.

24 CHAIRMAN PACKER: Or to do anything else.

25 DR. PINA: Or to do anything else.

1 CHAIRMAN PACKER: Okay. So Ileana is
2 proposing some wording. We're going to talk about the
3 wording in a second because that's modifiable by the
4 other issues, that it should be what might be called
5 a nonspecified indication. It's indicated for the
6 management of these patients. We'll talk about who
7 the patients are in a moment, without specifying what
8 the benefits of treatment are.

9 This is an important question. We'll take
10 it from either direction. Ralph, why don't you start?

11 DR. D'AGOSTINO: I would suggest putting
12 in the wedge pressure, and also that there is some
13 symptomatic relief possible, namely, the shortness of
14 breath. It doesn't have to be that detailed, but I
15 would put down what the study showed.

16 CHAIRMAN PACKER: Okay. Steve.

17 DR. NISSEN: I would focus on the group
18 that was studied in VMAC because I think that's the
19 best data that's here.

20 CHAIRMAN PACKER: But we're talking about
21 population in the next question.

22 DR. NISSEN: I'm sorry.

23 CHAIRMAN PACKER: Just what's the
24 indication.

25 DR. NISSEN: Yeah. Acute congestive heart

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1 failure in patients with dyspnea at rest.

2 CHAIRMAN PACKER: That's the patient
3 population.

4 DR. NISSEN: Yeah. I'm sorry.

5 CHAIRMAN PACKER: The only question is
6 does it say for the management of these patients or
7 should it say for the management of these patients to
8 do something, to lower wedge pressure or to improve
9 something.

10 DR. NISSEN: Oh, I see. To lower wedge
11 pressure and reduce symptoms.

12 CHAIRMAN PACKER: Okay. That's what Ralph
13 said to both. We'll talk about the patients in a
14 moment.

15 DR. LINDENFELD: I think we should say the
16 indication is for what it did, and that's to lower
17 wedge pressure and improve dyspnea.

18 CHAIRMAN PACKER: Okay. Jeff.

19 DR. BORER: I think the indication should
20 be for short-term treatment of people with acute
21 cardiac decompensation or, slash, heart failure.

22 CHAIRMAN PACKER: So full stop, no
23 modification.

24 DR. BORER: Full stop, no modification.
25 I think we should describe what's known and highlight

1 the areas where we know little so that we have
2 lingering concerns.

3 DR. LIPICKY: In the indication?

4 DR. BORER: No, no. In the label. No,
5 the indication --

6 DR. LIPICKY: Well, we're just talking
7 about the indication.

8 DR. BORER: Okay. I'd put a period after
9 heart failure.

10 CHAIRMAN PACKER: Al right. The only
11 question is do you put a period after heart failure or
12 do keep going. That's the question.

13 DR. HIRSCH: Say it again.

14 CHAIRMAN PACKER: Okay. We're talking
15 about patient population. We'll talk about dose,
16 we'll talk about all the safety things. We're going
17 to talk about that in a second. Here's the question.

18 Is the drug indicated for the short-term
19 intravenous treatment of something for something? Is
20 it indicated for the treatment of acute decompensated
21 heart failure, period, or for the acute -- short-term
22 treatment of acute decompensated heart failure to
23 lower wedge pressure, or to lower wedge pressure and
24 reduce symptoms?

25 In other words, there's three

1 possibilities. You can stop the indication after
2 heart failure, after wedge pressure, or after
3 symptoms.

4 DR. GRABOYS: Stop it after congestive
5 heart failure, period.

6 CHAIRMAN PACKER: Stop it after congestive
7 heart failure, period. Okay. Alan.

8 DR. HIRSCH: I think I'd have to go to the
9 end of your sentence with symptoms and wedge pressure.

10 CHAIRMAN PACKER: No, didn't you say that
11 a drug shouldn't be -- oh, you said for both. It
12 wouldn't be just a drop wedge pressure.

13 DR. HIRSCH: Both.

14 CHAIRMAN PACKER: Oh, okay. I just wanted
15 to make sure.

16 Ileana, clarify again?

17 DR. PINA: I would stop after acute heart
18 failure.

19 CHAIRMAN PACKER: Okay.

20 DR. ARTMAN: Yeah, I would stop after
21 acute heart failure, acute decompensated heart
22 failure.

23 CHAIRMAN PACKER: Okay. Marv.

24 DR. KONSTAM: I'd put it all in.

25 CHAIRMAN PACKER: Okay. I'd probably stop

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1 after acute heart failure.

2 The Committee is clearly split on this.

3 DR. LIPICKY: That's fine. So are we.

4 (Laughter.)

5 DR. HIRSCH: Can I make my case and shift
6 the Committee?

7 CHAIRMAN PACKER: Sure.

8 DR. HIRSCH: My concern is that in the
9 real world, not the excellent VMAC investigators, not
10 the members of this panel, not the members of this
11 audience, people still do get confused in the
12 community about what they're treating and the goals of
13 treatment in heart failure.

14 I mean, I'm concerned that we're still
15 talking low output, high output, forward flow, back
16 pressure. I think having them focus on the VMAC
17 population will preserve the best efficacy of the
18 medication and preserve safety.

19 I would remind people. Anybody convinced?

20 DR. LIPICKY: No.

21 CHAIRMAN PACKER: Okay. Who should be --
22 what is the target population? How do you describe
23 the patients who should receive this drug?

24 Ileana.

25 DR. PINA: Patents who present with

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1. dyspnea at rest and elevated wedge pressures, whether
2. measured or strongly suspected, regardless of
3. etiology.

4. CHAIRMAN PACKER: Regardless of etiology?

5. DR. PINA: Regardless of etiology. we
6. talked about excluding the patients with restrictive
7. cardiomyopathies and the patients that Marv had talked
8. about excluding.

9. CHAIRMAN PACKER: Okay.

10. DR. PINA: The database has ischemics,
11. non-ischemics. It has all sorts of patients.

12. CHAIRMAN PACKER: Okay.

13. DR. LIPICKY: Does the phenotype of wet
14. and lukewarm include everybody that you said?

15. DR. PINA: This is the wet and warm
16. population primarily.

17. DR. LIPICKY: And that means elevated
18. tubular pressures.

19. DR. PINA: It means elevated filling
20. pressures and a pretty well preserved cardiac index.

21. DR. LIPICKY: So if I see an elevated
22. jugular pressure, I can figure the whatever you're
23. measuring with that catheter that's up to --

24. DR. PINA: With other things.

25. CHAIRMAN PACKER: But it can't just be

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1 warm and wet, with all due respect, because it could
2 be used in conjunction with another drug in people who
3 are cool and wet, right?

4 DR. PINA: Well, this population was warm
5 and wet. This population was wet. The wedge was 28
6 and the index --

7 CHAIRMAN PACKER: Okay.

8 DR. LIPICKY: I take back what I said.

9 CHAIRMAN PACKER: Here's the proposal.
10 Ileana, I'm going to -- my sense is that your proposal
11 to say regardless of etiology could get into some
12 issues here. I'm going to take the Chairman's
13 prerogative of curtailing that and then seeing if we
14 want to add it.

15 Ileana is proposing that the indication be
16 patients -- I'm sorry. What kind of patients are we
17 talking here?

18 DR. PINA: These are patients who have
19 acute decompensated heart failure with dyspnea at rest
20 and elevated wedge pressure, whether measured or
21 presumed.

22 CHAIRMAN PACKER: Okay. So it's acute
23 decompensated heart failure with dyspnea at rest and
24 elevated wedge pressure either measured or clinically
25 estimated or however. I think that's the word they

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1 used.

2 Okay. Anyone want to disagree with that?

3 DR. KONSTAM: I'll disagree. I would put
4 in in patients with low ejection fractions, and let me
5 clarify that that wouldn't imply that you have to
6 measure the ejection fraction before you start the
7 drug, but I would want it communicated that -- you
8 know, Ileana sort of said it about the hypertrophic
9 patients, but really the way of saying that in the
10 real world is just saying approve it in patients with
11 low ejection fractions.

12 PARTICIPANT: With presumed systolic --

13 DR. KONSTAM: Yeah, presumed systolic
14 dysfunction, and that's really the population where we
15 have the vast, vast majority of our information, and
16 I think we have god reason to be concerned that it
17 just doesn't apply in the others.

18 DR. PINA: Well, Marvin, if we're not
19 going to totally exclude the acute coronary syndromes,
20 how do you know that some of those acute coronary
21 syndromes don't have --

22 DR. KONSTAM: Well, I didn't say whether
23 we --

24 DR. PINA: -- ejection fractions?

25 DR. KONSTAM: Well, I'm not sure. I don't

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1 know whether we really addressed that in this.

2 DR. PINA: Well, but that population may
3 be in there as well.

4 DR. KONSTAM: Well, I don't know how to
5 handle that. I'm not sure this is the place to handle
6 it.

7 DR. LIPICKY: Let us worry about that.
8 You I don't think will be able to settle that real
9 quickly. So we'll take care of it.

10 CHAIRMAN PACKER: Okay. The proposal is
11 -- let's make sure we got it -- acute decompensated
12 heart failure with dyspnea at rest, with elevated
13 filling pressures measured or clinically estimated.

14 I think there's a comfort level with that.
15 How many of you -- no?

16 DR. BORER: Can I just ask for
17 clarification? We just voted on what the indication
18 is. Now we're restating the indication with some
19 other descriptors. I thought we were talking about
20 the population.

21 CHAIRMAN PACKER: No, we talked about the
22 component of the indication that describes what the
23 drug is for. Now we're talking about the component of
24 the indication that describes for whom it should be
25 given.

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1 So let me just make sure. We have
2 actually two slightly different proposals. It sounds
3 like everyone is comfortable with dyspnea at rest or
4 elevated pulmonary wedge pressure. The only question
5 is is there an additional modifier.

6 DR. BORER: I really hate to sound like
7 the iconoclast in the group because I really shouldn't
8 be, and I'm not, but I think we're being awfully
9 restrictive here. We have the VMAC study. That is
10 not the totality of the data that was put before us.

11 What we saw from VMAC is that you can
12 reduce the wedge pressure, and you can make people
13 feel better at the same time as you're doing that.
14 The evaluation and the management of patients with
15 heart failure I think is a lot more complex than that,
16 and I don't think we should be quite so restrictive in
17 a label to say that the only thing that people can do
18 with a drug that does these things is treat exactly
19 the patient who is admitted to the VMAC study. You
20 know, I think that's too restrictive. I don't think
21 we know enough to do that.

22 I think that we would be better served if
23 we describe what's known and note what's not known
24 that we're concerned about rather than try to micro
25 manage the people who are going to get the drug.

1 CHAIRMAN PACKER: Jeff, it wasn't that
2 long ago, just a few minutes ago, when Marv suggested
3 and everyone agreed that one of the qualifications for
4 use should be an elevated pulmonary wedge pressure
5 measured or clinically estimated.

6 So the only difference between Ileana's
7 proposal and the proposal that we felt comfortable
8 with a few minutes ago is the qualification of dyspnea
9 at rest.

10 DR. BORER: I don't want to take
11 everybody's time with this, but I didn't think that's
12 what happened. I think that Marvin raised a concern
13 about giving the drug to people who have low wedge
14 pressures. I don't know how you estimate a wedge
15 pressure clinically. So you know, I think that
16 Marvin's concern is a very important one and ought to
17 be stated somewhere in whatever instructions for use
18 are given, but I don't know. How do you estimate a
19 wedge pressure clinically?

20 CHAIRMAN PACKER: Gee, I don't know.
21 Shortness of breath at rest, riles all the way up. I
22 mean there are ways.

23 DR. PINA: Can't lie recumbent.

24 CHAIRMAN PACKER: How does the rest of the
25 Committee feel about this?

1 DR. KONSTAM: Well, I don't know exactly
2 where -- I mean I'm not sure whether we need to micro
3 manage, Ray, about exactly where. I don't think we
4 need to wordsmith this. I mean, I think the sense is
5 that, you know, there might be a problem if you gave
6 this drug to a patient who had a normal or low wedge
7 pressure, and as long as he takes that message home
8 and makes sure that that's somehow communicated in the
9 packet insert, I'd be satisfied with that.

10 I don't know how to say it or where to say
11 it.

12 CHAIRMAN PACKER: Okay. Any other issues
13 related to patient population that you would think
14 requires some description or qualification?

15 Okay. If not, dose and duration of
16 treatment.

17 DR. KONSTAM: Well, but did we deal with
18 the ejection fraction thing?

19 DR. LIPICKY: Yeah. It's noted that that
20 has to be dealt with.

21 DR. KONSTAM: Okay.

22 DR. LIPICKY: And I don't know how to deal
23 with it, but we will deal with it somehow.

24 CHAIRMAN PACKER: Dose and duration of
25 treatment. Ileana.

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1 DR. PINA: That's where it gets tough
2 because the dose that I would have to recommend would
3 be the dose used in the VMAC trial with a bolus and
4 the infusion rate that was used in the VMAC trial.

5 I don't know how to recommend up-titration
6 since the non-catheterized group was not up-titrated,
7 and I imagine the majority of these patients will not
8 have a catheter in. So it would have to be at the
9 fixed dose used in the VMAC trial.

10 CHAIRMAN PACKER: So you're saying the
11 drug should be approved for a one recommended dosing
12 regimen, two micrograms per kilogram bolus, followed
13 by .01 microgram per kilogram per minute, period.

14 DR. PINA: I don't see any other way to do
15 it, except that you may want to say in the labeling
16 that the group of patients who had a catheter in were
17 up titrated in the following fashion, with the such-
18 and-such bolus and the such-and-such increments.

19 But, again, the number of patients that
20 were actually incremented were small, even in the
21 adjustable dose.

22 CHAIRMAN PACKER: Yeah. You could say
23 that higher doses should not be used unless the
24 patient is invasively monitored.

25 DR. PINA: But that's, again, restricting

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1 the population to getting invasively monitored, which
2 may not be bad for some of these patients, but that's
3 my personal opinion.

4 CHAIRMAN PACKER: Joann.

5 DR. LINDENFELD: Invasive monitoring
6 didn't prevent hypotension at higher doses.

7 CHAIRMAN PACKER: Right.

8 DR. HIRSCH: Or just say higher doses can
9 be used according to the discretion of the physician
10 with appropriate monitoring of blood pressure and
11 renal function, as we do for other drugs.

12 CHAIRMAN PACKER: Jeff.

13 DR. BORER: I think that my concerns are
14 similar to Ileana's. I mean, we know that one dose
15 regimen was reasonably tolerated. I think we know
16 very little about the higher doses, except that
17 problems could occur. They didn't occur in most
18 people, but that they can occur, and I think that
19 here, again, I think that Ileana's point is well
20 taken, that we should say that this is the dose, point
21 out that higher doses have been used, but that there's
22 a great deal not known and some concern about risk,
23 and with the titration regimen that they used in VMAC
24 being noted as part of that statement.

25 I think that is one were to do that, one

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1 might also want to say that if you start out at higher
2 doses than the one that's indicated, there's some
3 suggestion of renal problems and hypotension.

4 CHAIRMAN PACKER: Steve. I'm sorry.

5 DR. NISSEN: I think we should limit the
6 labeling to the VMAC dose for one particular reason.
7 It's not that you can't use higher doses. It's that
8 because of the pharmacokinetic and pharmacodynamic
9 effects that we've seen here, the problem is if you
10 get in trouble with this drug, it's a lot harder to
11 get out of trouble than it would be with a drug like
12 nitroglycerine, and so we're taking much greater risks
13 with allowing or with recommending higher doses.

14 DR. KONSTAM: Which VMAC dose are you
15 talking about, the .01?

16 DR. NISSEN: Yes. And the reason I -- I
17 mean, again, if the drug had a three-minute half-life,
18 I would feel differently, but I'm concerned about the
19 ability to get into trouble and then have trouble
20 getting out of trouble.

21 DR. KONSTAM: Yeah, I also want to add
22 that it was proposed to us that, you know, gee, we
23 should probably be less worried about the higher doses
24 if you titrate up gradually, but we don't really have
25 data to support that, you know, and I think in VMAC it

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1 was 13 patients who got to a dose above .015. So
2 although it makes sense, we don't have the data to
3 support that.

4 That will be a difference between just
5 starting on the dose.

6 CHAIRMAN PACKER: Okay. What I hear is a
7 proposal that there should be one dosing regimen, two
8 micrograms per kilogram per minute bolus, followed by
9 .01 micrograms per kilogram per minute.

10 DR. KONSTAM: I'd be comfortable going up
11 to .015.

12 DR. PINA: Yeah, but the only way you get
13 there is by a second bolus.

14 DR. LIPICKY: We've got it, Milton. You
15 don't have to worry --

16 CHAIRMAN PACKER: I don't have to worry
17 about this too much?

18 DR. KONSTAM: Thank you, Ray.

19 CHAIRMAN PACKER: Thank you.

20 DR. PINA: Thank you, Ray.

21 CHAIRMAN PACKER: We have need for
22 central monitoring. We'll go to mortality in a
23 moment.

24 Oh, I'm sorry. Duration of treatment.
25 How long should people get this drug?

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1 DR. PINA: Well, in the VMAC trial, 487
2 patients had it for a 24-hour infusion. So I would
3 say for the short-term treatment up to 24 hours,
4 and --

5 CHAIRMAN PACKER: Some people got it for
6 more than 24 hours.

7 DR. PINA: Yeah, but it was a small amount
8 of patients that got it.

9 CHAIRMAN PACKER: Right.

10 DR. PINA: The vast majority had it for 24
11 hours or less.

12 CHAIRMAN PACKER: So the patients should
13 never get this drug for more than 24 hours?

14 DR. PINA: No, I didn't say that. I said
15 that --

16 DR. LINDENFELD: The mean is 36.

17 DR. PINA: -- for short-term treatment up
18 to 24 hours, and just state like we have. Other
19 patients --

20 CHAIRMAN PACKER: No, that's not the way
21 -- no, no. There's a recommended dose which we have
22 struggled with, and then there is some description
23 about what can or cannot be done or should or
24 shouldn't be done with respect to duration.

25 The indication, this doesn't appear in the

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1 indication. This is instructions for use.

2 DR. PINA: I would say can be given up to
3 24 hours, and leave it at that.

4 CHAIRMAN PACKER: Okay. Let's have
5 discussion. Jeff.

6 DR. BORER: Well, I share Ileana's
7 concern, but I wouldn't make the label quite so
8 restrictive. I think we do have information about
9 what happens beyond 24 hours in a reasonable number of
10 patients. I think I just heard somebody say that 36
11 hours was the mean duration that was given in the
12 trials that we saw.

13 I think we ought to say just as Ileana did
14 initially that it's indicated for short-term
15 administration and say what's known. A lot of people
16 are treated for 24 hours. We know this. There's
17 limited information beyond that, you know. So many
18 have been treated for 48 hours, and there's not much
19 known beyond that, and you know, you move at your own
20 peril.

21 DR. KONSTAM: Could we just get reminded
22 about what percentage, how many patients have been in
23 the database treated beyond 24 hours or between 24 and
24 48? How about just clarifying that? How many, yeah?

25 DR. HORTON: Even in VMAC, just to

1 clarify, 63 percent of the patients were treated for
2 24 to 72 hours, and then there were an additional six
3 percent who were treated for longer than 72 hours.

4 So I think the issue is if you're treating
5 a patient and you think they're doing well, you don't
6 want to be told that after 24 hours you have to stop
7 the drug.

8 DR. KONSTAM: Sixty-three percent were
9 treated beyond 24 hours?

10 DR. HORTON: Yes, 24 --

11 CHAIRMAN PACKER: Wait, no.

12 DR. HORTON: -- to 72 hours, 24 to 72
13 hours.

14 CHAIRMAN PACKER: Does the 63 --

15 DR. KONSTAM: That's beyond 24.

16 CHAIRMAN PACKER: -- correspond to over 24
17 or over 27?

18 DR. HORTON: Over 24 hours.

19 CHAIRMAN PACKER: What is it over 27?

20 DR. HORTON: That I don't know.

21 DR. GRABOYS: Twenty-four is too
22 restrictive. I think in patients recompensated, doing
23 well, we're not going to rush them off the drug.

24 DR. KONSTAM: No, but I think we should,
25 you know, talk about indicating it from what we know,

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1 and then if people want to use it longer, they use it
2 longer. And I'm not --

3 CHAIRMAN PACKER: How about if we not
4 impose a restriction and say there is limited
5 experience with this drug with infusions greater than
6 24 hours?

7 DR. KONSTAM: Brilliant.

8 CHAIRMAN PACKER: Anyone disagree?

9 DR. ARTMAN: I agree and I think --

10 DR. LIPICKY: Seventy-two hours is the
11 number.

12 DR. ARTMAN: I mean, the indication is for
13 acute decompensated heart failure. So how long does
14 that last? I mean if it's lasting five or six days,
15 you've got serious problems.

16 I don't want to be too restrictive with
17 this either, and I think seventy-two hours is a
18 reasonable window.

19 DR. HIRSCH: Seventy-two hours.

20 CHAIRMAN PACKER: Anyone disagree with 72
21 hours?

22 DR. LINDENFELD: We just said 60 percent
23 went between 24 and 72. How many beyond 48?

24 CHAIRMAN PACKER: No, no, no.

25 PARTICIPANT: Efficacy comes into play

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1 also.

2 DR. LINDENFELD: What percent beyond 48?

3 CHAIRMAN PACKER: Sixty-three percent is
4 up to 27 hours. No?

5 DR. LIPICKY: No.

6 DR. LINDENFELD: But we don't know how
7 many -- what percent after 48 hours? What percent of
8 the patients got the drug after 48 hours? Because the
9 mean duration was 36.

10 DR. NISSEN: I think the exposure of
11 patients was significant out to 72 hours, and so I
12 think that that number makes a lot of sense to me, and
13 that's what I think you're proposing, and I would
14 support it.

15 DR. LIPICKY: I think we can look at the
16 data, and we can figure out what the distribution was.

17 DR. KONSTAM: Do we know something about
18 efficacy at 72 hours?

19 DR. LIPICKY: Well --

20 DR. KONSTAM: Well, if we don't know
21 anything about efficacy at 72 hours, how could we be
22 recommending indications?

23 DR. LIPICKY: We only know about efficacy
24 at three.

25 DR. KONSTAM: Well, but we have good data

1 at 24.

2 DR. LIPICKY: No. We only know that you
3 have symptom relief at three hours.

4 CHAIRMAN PACKER: No, you have some data
5 at 24 hours versus nitroglycerine, which may be
6 placebo.

7 DR. LIPICKY: Okay.

8 CHAIRMAN PACKER: All right.

9 DR. LIPICKY: You know, but those were
10 borderline.

11 CHAIRMAN PACKER: We've seen worse, Ray.

12 DR. LIPICKY: But I don't think the
13 question is a reasonable question.

14 DR. HIRSCH: It's not entirely moot
15 though. The reality is we have very, very short-term
16 efficacy data. None of us presume additional safety
17 concerns, but we also don't know if there's continued
18 efficacy or technical access in there, both care and
19 cost constraints.

20 CHAIRMAN PACKER: You'll work it out.

21 DR. LIPICKY: Yeah.

22 DR. PINA: Can I ask the sponsor one more
23 time if you can possibly give me how many patients
24 went from 24 to 72 hours? In other words, how many
25 patients did two days and how many patients did three

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1 days?

2 You said 63 went 24 to 72 hours, but that
3 could be 50 at 24 and ten at 48.

4 PARTICIPANT: Twenty-five, 25 shows the
5 breakdown numbers.

6 DR. HORTON: I don't have it exactly like
7 that, but I have the 75th percentile is 44 hours. So
8 25 percent of the people were treated for more than 44
9 hours. I don't have it exactly as day one to day two.

10 CHAIRMAN PACKER: Why don't we leave this
11 to the division? They'll figure it out.

12 Okay. Need for central monitoring. Who
13 would like to propose that this drug be used only in
14 or perhaps in some requirement for central monitoring
15 either in some or in all patients?

16 Ileana?

17 DR. PINA: I don't think you can recommend
18 central monitoring at all.

19 CHAIRMAN PACKER: Okay. Anyone disagree?

20 Okay. Any -- I'm going to leave mortality
21 to the end -- any special warnings or
22 contraindications? And this could be anything that
23 you want to say.

24 Special warnings, if I remember, Ray, help
25 me out here. We have talked about some concerns. Is

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1 this to ask us whether the concerns are sufficiently
2 significant that we would make it a special warning,
3 put it in warning or put it in a black box or --

4 DR. LIPICKY: Well, I guess we have heard
5 your concerns, and these are scattered, and this is
6 there to just say are you worried about anything that
7 you have been worried about that you've stated. I
8 think that's the way to look at it.

9 CHAIRMAN PACKER: Okay.

10 DR. LIPICKY: Anything else? Anything
11 that you haven't said, "I'm worried about"?

12 CHAIRMAN PACKER: Anything else?

13 Nothing else.

14 DR. PINA: I think we've mentioned all the
15 concerns here.

16 CHAIRMAN PACKER: Okay. Last question.
17 Half of you said you were not concerned about
18 mortality. Half of you said you were a little
19 concerned about mortality. How many of you would say
20 that some mention of mortality, either a point
21 estimate, confidence intervals, or something?

22 Not to say that there was a worry about
23 it; that some description about the effect of
24 mortality should appear in labeling. It could be yes,
25 no, some modifier. That's what we're being asked.

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1 Ileana.

2 DR. PINA: My sense is that I wouldn't put
3 anything about mortality in the label. This is a
4 short-term use drug, and I think we've been
5 comfortable with what we've seen. At least I have.
6 I wouldn't put anything.

7 CHAIRMAN PACKER: Okay. Anyone disagree?

8 Okay. So those of us who were a little
9 worried about mortality are not sufficiently worried
10 about mortality that we think that anyone else needs
11 to be a little worried.

12 DR. LIPICKY: That's fine, and my smile is
13 very -- don't pay any attention.

14 CHAIRMAN PACKER: Okay. Last -- I think
15 we've done. Last question. Should nesiritide be
16 approved for the treatment of decompensated heart
17 failure?

18 I think we have had adequate discussion on
19 this question. Ileana, your vote on this?

20 DR. PINA: I think with all the caveats
21 that we have stated and with all the statements that
22 we have given, then yes.

23 CHAIRMAN PACKER: Okay, and we'll start
24 from -- we'll poll the vote. Why don't we start with
25 Marv and go all the way down?

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1 DR. KONSTAM: Yeah. I'm going to vote for
2 approval, and I'll just say I was one of the three
3 people who voted against at the last meeting, and my
4 reasons for it, you know, really were that there were
5 adverse events, and I didn't know how to weigh those
6 against some reasonable comparator, and at least the
7 doses used in this trial, I'm pretty comfortable with
8 it, and that's why I vote for approval.

9 DR. ARTMAN: I think the sponsor is to be
10 commended, and they've done a really nice job of
11 bringing this back to us, and I would say, yes, it
12 should be approved.

13 DR. HIRSCH: I would echo those sentiments
14 exactly.

15 DR. GRABOYS: Approval.

16 CHAIRMAN PACKER: Jeff?

17 DR. BORER: Yes.

18 DR. LINDENFELD: Yes.

19 DR. NISSEN: I need to explain my answer
20 here. I know it's late, but first of all, let me
21 compliment the sponsor for what I think was really an
22 excellent presentation, very responsive, and I think
23 answered a lot of our questions.

24 I also tell you that I'm very sympathetic
25 toward vasodilator drugs for acute and chronic

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1 congestive heart failure, and I particularly think
2 there are some important advantages to expanding
3 options here, mainly because it may allow more
4 physicians not to use inotropic agents to treat this
5 syndrome, which I am very concerned may actually
6 produce more harm than good.

7 I think you've shown efficacy
8 unequivocally, and I think it's well done. Obviously
9 it's a very difficult trial, but I think you met all
10 the benchmarks both on wedge pressure and on symptoms,
11 and I think that that was clearly well done.

12 I do have, however, major safety concerns
13 about the agent, and I want to make sure that I'm very
14 clear about this.

15 First of all, I do think there's a narrow
16 therapeutic index, narrower than a lot of the drugs
17 that we use.

18 I think the evidence that there was more
19 prolonged hypotension in those people that got
20 hypotensive is pretty unequivocal.

21 I think a drug -- if you were going to
22 design an intravenous drug for heart failure, you
23 would not want a drug with an 18-minute half-life
24 because if you have to wait five half-lives for the
25 drug to go away, that's about 90 minutes, and even if

1 you say, "Well, I'm not going to wait five half-
2 lives," you're still talking about an hour or so
3 before the drug disappears, and these are very, very
4 ill patients who if they get into trouble can spiral
5 down and get into a lot of trouble.

6 And the exposure that we know about here
7 is still relatively limited patients studied by very
8 good investigators in a very optimal setting. And I'm
9 worried about when and if this drug gets out in the
10 general community, that people are going to get in
11 trouble with the agent.

12 Therefore, I am prepared to vote for
13 approval, but only if there is a black box warning
14 that say something like this, and I'm not necessarily
15 very good at writing these: "this agent may produce
16 moderate or severe hypotension at recommended doses,
17 which may be more prolonged, lasting greater than 60
18 minutes, than typically seen with intravenous
19 nitroglycerine."

20 And I want that there because I think it
21 protects patients. I think it actually protects
22 everybody because it waves a red flag in front of the
23 faces of the practitioners that may be used to other
24 intravenous vasodilators, where if you turn it off,
25 the drug is gone pretty quickly.

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1 So I can only support approval if there is
2 such a black box warning around the drug.

3 DR. D'AGOSTINO: Yes.

4 CHAIRMAN PACKER: Let me put my vote in.
5 I would vote for approval, and let me also in doing so
6 respond to Steve's concern.

7 I share Steve's concerns, but, Steve, I
8 think your concerns are inherent to all intravenous
9 drugs that have half-lives that are meaningfully
10 longer than those that we're used to, like nitro --
11 nitroglycerine is very short. Nitroprusside is very
12 short. Dobutamine is very short.

13 We have drugs out there that have longer
14 half-lives now like IV Milrinone, a much longer half-
15 life. People get into trouble with that drug.

16 And I think that there has to be an
17 educational process in place here about how to use
18 this drug. I think the sponsor, to act responsibly
19 needs to tell people what you have just said, which is
20 that hypotension can occur, and hypotension can occur
21 to a degree which is far longer than what they might
22 expect from a typical IV drug.

23 A black box warning is usually reserved
24 for situations where there is demonstrated harm, and
25 I guess I haven't seen that sufficient degree of

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1. demonstration.

2. Maybe if there is an insufficient
3. educational process, reports will come in from the
4. field of such irreversible harm, and therefore, my
5. sense is that what you propose if the educational
6. process is insufficient may occur.

7. I think at this particular point in time,
8. your statement should probably serve as a very strong
9. suggestion or warning to the sponsor to say, "Please,
10. please, teach physicians about this particular risk
11. because they're not apt to know about it. They're apt
12. to think about IV drug therapy as you turn it off and
13. it's gone, and that's not true with this agent."

14. So to obviate the need for Steve's warning
15. coming true, a real educational effort needs to be
16. made to make sure that physicians know about this, and
17. maybe that's what we mean about a warning. I would
18. not recommend a black box, but --

19. DR. LIPICKY: No, I understand.

20. CHAIRMAN PACKER: -- a sufficiently strong
21. encouragement to the sponsor --

22. DR. LIPICKY: I understand --

23. CHAIRMAN PACKER: -- that this is
24. something that's important.

25. DR. LIPICKY: -- that there ought to be

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1 some kind of proactive risk management you're talking
2 about.

3 CHAIRMAN PACKER: Oh, I'm so sorry.
4 Ralph.

5 DR. D'AGOSTINO: Yes.

6 CHAIRMAN PACKER: I'm so sorry.

7 DR. LIPICKY: We heard that loud and
8 clear.

9 DR. NISSEN: Just to comment a little
10 further, I mean I understand, and obviously there is
11 a lot of subtlety in this, but I want to be really
12 clear here and send up this red flag that the
13 investigators in this study were real pros. I mean,
14 I looked at the list of people doing this. They're
15 people who treat congestive heart failure for a
16 living, and they're very good, and they know how to
17 manage, you know, these kinds of patients.

18 And my concern would be it's a lot easier
19 to come back with Phase IV data that says the drug is
20 safe and take a warning away than it is to wait until
21 there is trouble and add it on later.

22 DR. LIPICKY: Okay. We hear you loud and
23 clear.

24 CHAIRMAN PACKER: Okay. Yes?

25 DR. BORER: You know, we just voted in a

1 certain way, and that's fine, but is it reasonable to
2 ask whether anybody on the Committee would mandate
3 what Steve just said, that is, specific suggestion for
4 Phase IV?

5 CHAIRMAN PACKER: We have an insufficient
6 quorum to answer that question.

7 We are adjourned.

8 (Whereupon, at 5:20 p.m., the meeting in
9 the above-entitled matter was concluded.)

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CERTIFICATE

This is to certify that the foregoing transcript
in the matter of: CARDIOVASCULAR AND RENAL DRUGS
 ADVISORY COMMITTEE MEETING

Before: FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND
 RESEARCH

Date: FRIDAY, MAY 25, 2001

Place: NATIONAL INSTITUTES OF HEALTH
 ROCKVILLE, MARYLAND

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

Rebecca Davis