

1 normal pace is not to a super normal pace, and you may
2 have the same severity of PPH, but you're not anywhere
3 near as limited based on a six minute walk test
4 because you don't walk the same way that I walk.

5 So I think that's an inherent problem in
6 using something like the six minute walk test alone.
7 I think exercise an issue because that is one of the
8 clear manifestations of the disease, but it goes so
9 far beyond it.

10 So I think using the composite of the Borg
11 and the walk gives a real better picture. If after
12 treatment you say I'm really not walking much farther,
13 but I feel a whole lot better doing this, I'd say
14 that's a real effect and a meaningful effect.

15 DR. LIPICKY: I'm sorry. Because of the
16 answers, I have two more questions.

17 (Laughter.)

18 DR. RICH: I get myself in trouble.

19 DR. LIPICKY: So you do agree that it's
20 reasonable that, you know, when you get a body of data
21 from a clinical trial, if you know what you're doing,
22 you can make a good story out of anything, right? So

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 you've got to have some kind of primary endpoint upon
2 which everyone agrees.

3 So what do you do then if everyone has
4 agreed to a lousy primary endpoint and you don't quite
5 make it?

6 DR. KOCH: Well, let me try to help on
7 this. Again, Gary Koch.

8 Walking distance would have been a
9 perfectly fine primary endpoint and would have
10 shown --

11 DR. LIPICKY: If you won.

12 DR. KOCH: -- good effects had it been
13 possible to have exertion comparable in the two
14 groups, but when we look at the Borg score, we find
15 the exertion was substantially less in one group than
16 the other, and so that group actually was benefitting
17 two ways.

18 And because it was benefitting in two
19 ways, it was benefitting in a more moderate way in two
20 dimensions.

21 Now, the fact that the groups differ on
22 the Borg score then creates a scenario in which the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 walking distance becomes an imperfect endpoint, and
2 the only way out of that is to try to work out some
3 way in which the balancing of Borg and the walking
4 distance is put together.

5 There's a variety of ways to do that. One
6 way is the ranking method that we discussed. There
7 are a couple of other ways as well, but you have to
8 somehow consider the two concepts together.

9 And it also then makes the evaluation of
10 the other endpoints all the more important in terms of
11 signs and symptoms and dyspnea, fatigue, and
12 everything else.

13 But in this study, the issue is that
14 because there was a post baseline imbalance in
15 exertion, the impact on interpreting walk becomes more
16 difficult.

17 Now, the implication would have been more
18 complicated had it gone the other way. In other
19 words, you could have had a situation hypothetically
20 in which the treprostiniil group did wonderfully better
21 than the placebo group on walk, but you also found
22 that there was a substantial reversal on Borg. They

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 were basically, you know, almost exhausting themselves
2 to achieve that.

3 And there you would have had a clearly
4 significant difference on the walk, but you would have
5 had a contra indication coming from the Borg, and that
6 would have also been very difficult to interpret
7 because you would have then had to figure out how much
8 of the advantage with the walk had been bought with
9 the disadvantage on the Borg.

10 In this particular case, one does not have
11 that issue. One gets an advantage on both the Borg
12 and the walk, but because the two work against each
13 other, the impact is more modest. At least on the
14 walk it is. On the Borg, of course, it's very clearly
15 strong.

16 But walk would have been a fine endpoint
17 if you could have had equalness on the other.

18 DR. LIPICKY: Okay, but then the last part
19 of that same question was asked before and you sort of
20 answered it, but I didn't quite understand the answer.

21 So how do we put all of that together?
22 How should I react to all of that when it seems like

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 some people can find a good effect on six minute walk
2 and other people can't?

3 How do you explain that?

4 DR. KOCH: Well, I think you have to try
5 to figure out a way to put it together in either of
6 two ways. You either have to look at a total body of
7 evidence in terms of what the total body of evidence
8 is telling you across all the different criteria that
9 were looked at, or you have to figure out are there
10 ways in which you can unconfound the interpretation of
11 walk relative to the imbalance on exertion.

12 And the sponsor has tried to shed light on
13 each of those two ways of working, and that's
14 basically the total assessment that has to be weighed,
15 and one has to basically weigh everything because it
16 was not as if the walking distance in and of its own
17 right was assessed equitably in the two groups and
18 gave you a finding that is like the one that was seen.

19 So it's a total weight of evidence
20 assessment.

21 CHAIRMAN BORER: Alan, and then I have a
22 couple of final clarifications only before we move on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to safety.

2 Alan.

3 DR. HIRSCH: Ray, thank you for warming up
4 my audience. I'd like to thank the sponsor and Dr.
5 Rich for performing a prospective trial on a
6 population that obviously needs new therapies.

7 From my point of view, obviously we're
8 here to try to make our patients feel better and
9 improve quality of life, and so you may have answered
10 this, but I may have missed this. I want to go back
11 and re-express our concern regarding the efficacy
12 signal.

13 And I am going to mix up some of the
14 efficacy data with maybe adverse event data that may
15 come later, but bear with me.

16 My concern is that, you know, there's been
17 a question as to whether the efficacy signal is
18 relatively small or what is the clinical significance
19 of that signal, and so within that light, the
20 prostaglandin infusion itself, and prostaglandin is a
21 drug obviously that causes adverse effects that may be
22 well tolerated in some patients or to which there may

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 be a tolerance that occurs, but still there's the
2 potential for unblinding.

3 So I want to talk about unblinding in this
4 population because we are always balancing, as many
5 people said, hope in the patient and the physician for
6 something good to happen, and the disease doesn't get
7 better, I agree with you, in terms of its hemodynamic
8 arrangement.

9 We've shown actually in this database that
10 people get better on placebo. There are good days.

11 So with that preamble, I haven't seen the
12 database. Do we have any sense from the patients
13 themselves or from the physicians of their perceived
14 drug assignment to determine whether that signal is
15 due to unblinding from flushing, headache, local site
16 involvement?

17 DR. RICH: We did not do an exit poll of
18 patient or physician as to what they thought the
19 patient was on. What we have done, if you'd like to
20 see it, is an attempt to assess if unblinding did
21 occur, what impact might it have had on the results.
22 If you want to --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. HIRSCH: If there's some way that you
2 can convince me that unblinding didn't happen, I would
3 be happy.

4 DR. RICH: Okay. Let me say that we're
5 working from the premise that if unblinding occurred,
6 it was because of site pain because that was really
7 the dominant difference in terms of the side effects
8 of the two groups.

9 We didn't see a re excess of prostacyclin
10 type of side effects that we see with Flolan or
11 epoprostenol, and we don't know for sure why. It may
12 be the subcu. system. It may be that this drug
13 doesn't have the same dramatic flushing, et cetera.

14 But if you look at things like Dr. Barst
15 will go over jaw pain, jaw pain is almost universal
16 with epoprostenol. It's uncommon with treprostinil.

17 So let's assume that the drugs have some
18 differences, and let's assume that if unblinding
19 occurred, it would likely be on the basis of the
20 disparity of site pain in placebo versus control,
21 which is actually what the FDA raised as a question.

22 So if you will, given the fact that this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 is obviously not powered for this analysis, we looked
2 at it four ways. We say, okay, let's look at any site
3 pain or no site pain, and let's say those who had pain
4 present and those who had pain absent.

5 And these are the numbers in the active
6 placebo groups in the two sides, and then let's look
7 at the difference in distance by a six minute walk,
8 their Borg score, their dyspnea fatigue rating, and
9 their symptom change score, and the interaction.

10 And what we see is we fail to see any
11 interaction that having just pain present or absent
12 influenced these outcome measures.

13 Next.

14 Now, if you say, well, okay, a lot of the
15 people who had placebo had pain because the needle
16 hurts, so let's kind of look at severe pain, moderate
17 to severe pain, which was more likely to be in the
18 treated group than the active placebo group.

19 We had the exact same format here where
20 we're listing the different outcome measures, and
21 using moderate to severe pain present versus absent
22 and looking at the interaction, and once again we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 failed to see any strong interaction between the two.

2 Next.

3 DR. FLEMING: Excuse me. Can we go back?

4 DR. RICH: Yeah.

5 DR. FLEMING: Next slide.

6 DR. RICH: This was the first I'm showing.

7 DR. FLEMING: The next one.

8 DR. RICH: The next one. Okay.

9 DR. FLEMING: Twelve or 13 in the placebo
10 group and severe pain that are present.

11 DR. RICH: Yes.

12 DR. FLEMING: So there is really no
13 substantive data here to really assess the
14 interaction.

15 DR. RICH: Data --

16 DR. FLEMING: Essentially you're saying in
17 the severe pain assessment, present group, is there
18 the same level of difference, and you've got 12 people
19 in the placebo group.

20 DR. RICH: Granted this is the reporting.
21 This is the way it was reported. This is what we
22 have.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. FLEMING: It's what you have, and I
2 don't challenge that you had more. I'm just saying
3 it's extraordinarily difficult to draw that
4 conclusion.

5 DR. RICH: Understood. So what we're
6 doing is just looking at some sense of trends even
7 though there's absolute no power for that. Agreed.

8 DR. FLEMING: And, of course, it's not in
9 any way obviously random. These aren't baseline
10 subgroups where we randomize for comparability.

11 DR. RICH: Right, right.

12 I'll finish very quickly then. We did the
13 same thing -- next slide -- about reaction, which was
14 an even broader definition. So you could have a
15 little skin reaction without pain, and reaction
16 present versus reaction absent, the same outcome
17 measures, the same lack of interaction, a little
18 better balance.

19 And then finally we characterized it as
20 moderate to severe reaction versus no moderate to
21 severe reaction, and again, the same.

22 So to the extent that we really made an

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 attempt to see if unblinding occurred based on site
2 pain anyway, did that unblinding have a measurable
3 impact on the outcome measures? We couldn't detect
4 it.

5 And I would have liked to have seen exit
6 polls, but we don't have that.

7 DR. HIRSCH: We appreciate the effort.
8 One more quick question so that we can stay on
9 schedule, if I might. Again, quality of life --

10 DR. FLEMING: I just wanted to look at one
11 last thing on that last slide.

12 DR. RICH: The last slide?

13 DR. FLEMING: So in the symptom change
14 score, those people that had -- well, in essence
15 that's okay.

16 DR. RICH: Okay, okay.

17 DR. HIRSCH: Again, we're trying obviously
18 with this medication to help people feel better. So
19 really all of these various things like Gary said are
20 quality of life tradeoffs. So I want to talk about
21 the tradeoff sense here between symptom improvement
22 and the other thing that was alluded to, which is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 hospitalizations, which causes both an equality of
2 life tradeoff. It may not be measured during
3 hospitalization, but certainly it's there and a cost.

4 We may get to this later, but again, why
5 were patients on the active medication hospitalized at
6 almost equal rates if it wasn't for pulmonary
7 hypertension related matters?

8 DR. RICH: Okay. Can we go back first to
9 the slide that just showed the breakdown of
10 hospitalizations for the three categories? And then
11 we can deal with --

12 DR. HIRSCH: You must have more detail.
13 Something is going on.

14 DR. RICH: And then we can deal with that
15 other category. So I think that's number -- okay.

16 So this table, and you understand number
17 of patients and number of events because some patients
18 were hospitalized more than once, lists any
19 hospitalization, and let's focus on the patients, for
20 example, treprostiniil versus placebo, those that were
21 attributed by the investigator due to worsening
22 pulmonary hypertension or right heart failure, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 those for other reasons.

2 And so what you're asking me is what were
3 the other reasons that caused this. We have that.

4 DR. HIRSCH: Because even though we say
5 this is a small population of patients, once they're
6 effective treatments, obviously we as physicians seek
7 the diagnosis. The populations increases. We have
8 drugs on the market for larger populations, and these
9 effects are magnified.

10 DR. RICH: Okay. So this lists, and this
11 is patients. So there are two patients fatigue, two
12 dehydration. This is what was listed on the case
13 report form by the investigator as the reason for
14 hospitalizing the treprostnil group and the placebo
15 group.

16 CHAIRMAN BORER: Okay. Thank you, Dr.
17 Rich.

18 I have a couple more questions, too, I'm
19 going to hold until after Dr. Barst's benefit-risk
20 discussion, but you showed in your slide 42 rather
21 compelling p values when the more conservative
22 evaluation suggested by the FDA were used compared to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the prespecified evaluation with the rules that you
2 used, and those values don't correspond to what we
3 were given in the substance of the FDA medical
4 reviewer's comments that were sent to all of us.

5 In fact, by the approaches that the FDA
6 suggested, statistical significance was lost by at
7 least two of these approaches for walking distance
8 even for the pooled data.

9 So can somebody explain to me briefly why
10 there is such an apparent discrepancy between the
11 FDA's analysis of these data using their approaches
12 and your analysis using their approaches?

13 DR. ARNISON: Sure. Carl Arnison from
14 United Therapeutics.

15 What we did was to take our original
16 analysis method that we prespecified in the analysis
17 plan and then applied the reclassifications as done in
18 this slide. I believe what was done by the FDA
19 statistical reviewer was to apply his primary
20 analysis, which differed slightly in some ways from
21 ours.

22 And in fact, if he applied his analysis to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the data without reclassification, I think the p value
2 was somewhere around the order of .015 versus .0064.

3 CHAIRMAN BORER: Well, okay. The p values
4 I have in front of me here from the FDA are a little
5 different from that, but I think this is going to
6 require some detailed discussion, and you may want to
7 think about this and look at the FDA data and comment
8 on them just when we get to our final discussion

9 Ray, did you want to comment on that?

10 DR. LIPICKY: Yeah. I'm not sure you need
11 to spend very much time discussing that. What it says
12 is you get different p values depending on what you
13 assume, and that you can go in one direction or the
14 other from what the p values were for the primary
15 specified analysis.

16 And so then, you know, what are you going
17 to do?

18 CHAIRMAN BORER: Well, okay. It's just my
19 understanding is that the FDA approaches were used in
20 this slide 42 analysis.

21 DR. LIPICKY: Well, but different
22 judgments were made in who was selected and who was

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 not selected.

2 CHAIRMAN BORER: Okay.

3 DR. LIPICKY: And that's all, and so then
4 you'd have to get down to case by case why did you
5 make that decision.

6 CHAIRMAN BORER: Okay. It's going to get
7 too detailed to warrant a discussion right now.

8 A final question for you, and you may not
9 want to respond to this immediately, and you can later
10 if you like. In your analysis, you didn't present it
11 here, but in the book you sent us, there was an
12 interesting analysis that related dose to effect, and
13 it suggested that people who received higher doses had
14 greater effect, and I found that compelling.

15 And then I looked at the data that were
16 analyzed by the FDA and found that though your
17 analysis may, indeed, be correct, if you looked at
18 individual patients as they scaled up the dose, there
19 didn't seem to be a dose effect relation.

20 So I wonder if you can resolve that.

21 DR. RICH: Well, we can show you this type
22 of data two ways. You may have seen it, and so this

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 may not be more enlightening.

2 We do have a slide showing the dose and
3 the walk distance. Okay. This is measured at week
4 12, and this is mean change from baseline, and what
5 we've done is put them in four quartiles. So we have
6 the lowest quartile where the mean dose was in those
7 less than five, five to 8.2, 8.2 to 13, and this may
8 be what you're referring to that you saw, that those
9 who had the higher doses seem to perform better.

10 CHAIRMAN BORER: Right.

11 DR. RICH: The only other data that we had
12 that would be supportive of this is concentration
13 versus walk, where we measured serum concentration,
14 and there is this data, and again, you're seeing the
15 same trend being reproduced, those who had the highest
16 serum concentration -- again, this is mean change in
17 week 12 -- did better than those with the lower
18 concentrations.

19 CHAIRMAN BORER: Okay, but as you -- all
20 right. We won't go on with that now.

21 Why don't we hold any further discussion
22 about efficacy and let's hear from Dr. Barst about

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 safety and relation of benefit to risk?

2 DR. BARST: Thank you very much.

3 Treprostinil has been administered to 843
4 subjects or healthy volunteers who have been enrolled
5 in 15 clinical trials. Seven hundred and forty-three
6 of these 843 subjects were patients with pulmonary
7 arterial hypertension. Of these, 39 patients
8 participated in two acute hemodynamic studies, 01 and
9 02.

10 Four hundred and ninety-six patients were
11 enrolled in the three placebo controlled trials,
12 Studies 03, 04, and 05, and an additional 208 patients
13 were directly enrolled in the open label, long term,
14 compassionate extension study. Therefore, the open
15 label study, 06, consisted of 631 patients, 423
16 patients who completed the controlled trials and 208
17 patients were enrolled directly into the open label
18 study.

19 My presentation will focus on two sets of
20 patients. First, comparisons of treprostinil versus
21 placebo are based on the data derived from the 5496
22 patients enrolled in the placebo controlled trials.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Second, evaluation of the long term
2 effects of treprostinil are based on the 679 patients
3 of the total of 743 patients with pulmonary
4 hypertension who received chronic treatment with
5 treprostinil.

6 Next slide.

7 This slide summarizes the duration of
8 exposure in the 679 patients who received chronic
9 treatment with treprostinil. Of these 679 patients,
10 374 patients were treated with chronic treprostinil
11 for at least six months and 224 patients received
12 chronic treprostinil for at least one year.

13 The mean duration of exposure was 9.6
14 months. The longest exposure in the database filed
15 with the FDA through October 1st, 2000 was 2.3 years.

16 Next slide.

17 This slide summarizes the dose of the
18 treprostinil used during long term treatment with the
19 drug. Please remember that doses of treprostinil were
20 adjusted to alleviate symptoms while avoiding
21 intolerable adverse events. The mean dose of
22 treprostinil at initiation of treatment was 1.3

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 nanograms per kilogram per minute, and the dose was
2 gradually increased fairly rapidly during the first
3 three months and more slowly in patients treated for
4 more than six months.

5 The mean dose were 15, 24, and 30
6 nanograms per kilogram per minute at six, 12, and 18
7 months of treatment. This requirement for escalating
8 doses was not unexpected since a similar phenomenon is
9 characteristic of long term treatment with
10 epoprostenol.

11 Next slide.

12 This slide shows the adverse events
13 occurring with a frequency of more than ten percent in
14 patients enrolled in the placebo controlled trials and
15 in patients enrolled in the open label Study 06.

16 Please note that the pattern of adverse
17 events during long term treatment with treprostinil in
18 Study 06, which had an average exposure of 9.6 months,
19 is similar to the pattern seen in the placebo control
20 studies which had an average exposure of 2.7 months.
21 Therefore, long term treatment with treprostinil was
22 not associated with safety concerns beyond those

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 identified in the placebo controlled trials.

2 In both circumstances, the adverse events
3 associated with treprostinil fell into two distinct
4 categories, those related to a local reaction to
5 treprostinil at the infusion site and those related to
6 systemic effects that are characteristic of
7 prostacyclin therapy.

8 Next slide.

9 The most common adverse events associated
10 with the use of treprostinil were related to local
11 reactions of the infusion site, primarily pain or
12 erythema and induration.

13 These were observed in approximately 85
14 percent of the patients who received treprostinil and
15 in 26 percent of the patients who received placebo.

16 Next slide.

17 Systemic side effects characteristic of
18 prostacyclin therapy were also more common in the
19 treprostinil treated group than in the placebo group.
20 These include diarrhea, headache, nausea, jaw pain,
21 and vasodilatation.

22 However, these adverse events occurred in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 only ten to 30 percent of patients and generally
2 subsided despite continued treatment.

3 Next slide.

4 This slide summarizes the dose of
5 treprostinil received in patients at the time that
6 these adverse reactions had their first onset. The
7 data represent the percent of patients who reported a
8 specific adverse effect who experienced that event for
9 the first time at a specific dose.

10 For example, of patients who experienced
11 infusion site pain, 52 percent experienced such pain
12 for the first time at a dose of less than 2.5
13 nanograms per kilogram per minute.

14 Again, one can see two distinct patterns
15 of response. In fusion site pain or reactions were
16 generally observed during initiation of treatment
17 while patients were receiving low doses of
18 treprostinil.

19 In contrast, systemic side effects of
20 treprostinil therapy could be observed for the first
21 time at any dose of the drug.

22 Next slide.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 This slide summarizes the percent of
2 treated patients who reported a specific adverse event
3 during specific time intervals over the course of long
4 term treatment. This slide summarizes the data from
5 the 254 patients who have received treprostiniil for at
6 least 72 weeks as of May 1st, 2001.

7 For example, 88 percent of patients
8 reported infusion site pain at any time during the
9 period from day 2 through week 12, whereas only 43
10 percent of patients reported this adverse event from
11 any time from week 25 through week 48.

12 As can be seen, the frequency of adverse
13 effects seen during the first three months of
14 treatment generally decreased with increasing duration
15 of treatment, even though these patients generally
16 received increasing doses of the drug during the
17 follow-up period. This is true for both the local and
18 systemic reactions to the drug.

19 I want to emphasize that this declining
20 frequency is not due to patients dropping out because
21 of an adverse effect since all patients in this
22 analysis received treprostiniil for at least 72 weeks.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Hence, the adverse effects of treprostini
2 are not exacerbated by progressive increments in dose
3 that are characteristic of long-term treatment.

4 Next slide.

5 It should be noted that although some
6 adverse reactions were more common in the treprostini
7 treated group than in the placebo group, the frequency
8 of serious adverse events was similar in both groups.
9 This was also true if one confined the analysis to
10 deaths alone.

11 Next slide.

12 Despite the high frequency of adverse
13 events in both the placebo and treprostini treated
14 groups, the percent of patients requiring the
15 withdrawal of treatment because of an adverse event
16 was very low both in the placebo controlled trials
17 with an average duration of 2.7 months as well as in
18 the open label study with an average duration of 9.6
19 months.

20 this indicates that most adverse events
21 were mild in severity, self-limited and manageable.
22 Nevertheless, the frequency of withdrawal due to an

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 adverse event was higher in the treprostinil treated
2 group than in the placebo treated group, ten percent
3 versus three percent.

4 This difference was entirely related to
5 the occurrence of infusion site pain or reaction.

6 Next slide.

7 The occurrence of infusion site pain
8 reaction is, therefore, the primary safety concern
9 with the use of treprostinil in the treatment of
10 patients with pulmonary arterial hypertension. As a
11 result, it is worth spending a few minutes describing
12 the characteristics and management of this adverse
13 event.

14 Most patients who receive treprostinil
15 experience pain or inflammation at the site of
16 infusion, presumably related to a direct action of
17 treprostinil on local pain receptors or, in effect, on
18 vascular permeability.

19 The reaction is generally characterized by
20 pain, erythema on induration, but severity of the
21 response varies enormously from patient to patient and
22 even from infusion site to infusion site in the same

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 patient.

2 As you have already seen for the first
3 time when treatment with treprostinil is initiated,
4 and it's occurrence does not increase, and, in fact,
5 tends to decrease with continued treatment despite
6 increases in dose.

7 Therefore, infusion site reactions do not
8 generally limit the dose of treprostinil that can be
9 administered. Despite its very infrequent occurrence
10 and despite -- excuse me -- despite its very frequent
11 occurrence and its significant annoyance to patients,
12 in fusion site pain or reaction s were generally
13 manageable and were, therefore, tolerated in most
14 patients by relocating the infusion site, by using hot
15 and cold compresses, and by using over-the-counter
16 medications or prescription analgesics if needed.

17 Next slide.

18 This slide summarizes the most frequently
19 prescribed treatments for infusion site pain or
20 reaction. A wide variety of strategies and
21 medications were used to manage infusion site pain,
22 including those listed on this slide.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 In approximately 27 percent of patients,
2 narcotic analgesics were prescribed to treat infusion
3 site pain.

4 N e x t s l i d e .

5
6 However, most of these prescriptions were
7 written for PRN use only. Because of the way the case
8 report form was designed, we did not capture
9 information about actual use. Nevertheless, the data
10 collected on prescriptions are of interest.

11 The prescription of narcotic analgesics
12 vary greatly from center to center with about 40
13 percent of these 40 centers not prescribing narcotics
14 at all.

15 Furthermore, as might be expected from the
16 decreasing frequency of reports of pain during
17 prolonged treatment with treprostinil in the open
18 label extension Study 06, there was a corresponding
19 decrease in the number of patients who received
20 prescriptions for narcotics during the long term
21 study. This is shown on the next slide.

22 Twenty-seven percent of the patients

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 randomized to treprostinil in the 12 week placebo
2 controlled trials ere prescribed a narcotic analgesic
3 as compared with only 21 percent of the patients who
4 received treprostinil during an average of 9.6 months
5 of open label treatment.

6 Of note, most of these prescriptions were
7 for Schedule 3 drugs, such as tylenol with codeine or
8 Schedule 4 drugs, such as Darvon.

9 Only six percent of patients were
10 prescribed Schedule 1 or 2 narcotics, such as
11 meperidine, oxycodone, or fentanyl patch.

12 Next slide.

13 To assess the actual use rather than the
14 prescribed use of narcotic analgesics for treating
15 infusion site pain, investigators contacted 535 of the
16 545 patients who were taking treprostinil in the open
17 label Study 06 as of May 2001.

18 Although 21 percent of the patients in the
19 open label extension had been prescribed a narcotic
20 analgesic, the actual frequency of use of a narcotic
21 analgesic was lower. Eight percent of the patients
22 used a narcotic analgesic on the day immediately prior

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to contact, and 15 percent of the patients used a
2 narcotic analgesic at any time during the week
3 immediately prior to contact.

4 Only one percent of the patients had used
5 a Schedule 2 narcotic on the previous day, and only
6 two percent had used a Schedule 2 narcotic any time
7 during the previous week. These data suggest that
8 infusion site pain generally did not require treatment
9 with narcotic analgesics during long term therapy with
10 treprostinil.

11 Next slide.

12 It should be emphasized that long term
13 treatment with treprostinil has not been associated
14 with clinically meaningful changes in serum
15 electrolytes, renal or hepatic function, hemoglobin or
16 hematocrit, platelet count, coagulation parameters or
17 electrocardiographic intervals.

18 In addition, there have been no clinically
19 important drug interactions or idiosyncratic events.

20 Next slide.

21 Based on the data presented today and in
22 the briefing document presented to the committee, we

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 believe that the following conclusions are warranted.
2 In clinical trials carried out with treprostinil, the
3 adverse effects of the drug were related to its
4 pharmacologic properties and were generally not
5 serious.

6 Serious adverse events occurred with
7 similar frequency in the placebo and treprostinil
8 treated groups. Localized infusion site pain and
9 reaction were common, but generally were manageable
10 and did not limit increases in dose or require the
11 withdrawal of treatment.

12 Treprostinil was not associated with any
13 significant changes in laboratory parameters or end
14 organ toxicity.

15 Next slide.

16 Perhaps most importantly, treatment with
17 treprostinil is not associated with any of the
18 potentially life threatening adverse events that can
19 occur during treatment with epoprostenol, which is
20 presently the only drug approved for the treatment of
21 pulmonary hypertension.

22 These include risk of sepsis from the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 catheter, risk of thrombosis from the catheter, risk
2 of stroke due to paradoxical embolisms from the
3 catheter, risk of trauma and pneumothorax with
4 catheter placement, and risk of cardiovascular
5 collapse from brief interruption of the epoprostenol
6 infusion due to pump malfunction or dislodgement or
7 perforation of the catheter.

8 The epoprostenol package insert notes that
9 14 percent of epoprostenol treated patients have had
10 at least one episode of sepsis from a catheter
11 infection with a rate of a potentially fatal systemic
12 infection greater than 0.3 systemic infections per
13 patient per year.

14 In addition, because epoprostenol has a
15 very short half-life, one to two minutes
16 intravenously, as compared with three to four hours
17 for subcutaneous treprostinil, sudden interruption of
18 an infusion of epoprostenol can lead to rapid loss of
19 efficacy, which can also be fatal.

20 Treprostinil has not been associated with
21 any of these life threatening risks to date.

22 Next slide.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 In addition, unlike epoprostenol,
2 treprostinil is delivered using a micro infusion
3 device that is inserted by the patient at home using
4 a subcutaneous catheter. Unlike epoprostenol,
5 treprostinil is stable at ambient temperature and,
6 thus, requires no reconstitution or cold packs to
7 prevent degradation.

8 Indeed, because of the many risks and
9 inconveniences of epoprostenol therapy, many patients
10 who otherwise would be candidates for epoprostenol are
11 not recommended for epoprostenol treatment or they
12 decline treatment with epoprostenol if it is offered.

13 At the present time, there is no effective
14 therapy for these patients.

15 Next slide.

16 In the context of this unmet need, it is
17 important to note that treatment with treprostinil
18 produces clinically meaningful improvements in
19 exercise tolerance assessed by the distance traversed
20 and the symptoms experienced during a six minute walk,
21 as well as improvements in symptoms of pulmonary
22 hypertension and hemodynamic variables.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Next slide.

2 What does this mean for patients with
3 pulmonary hypertension? For many years, it has been
4 difficult for both patients and physicians to weigh
5 the benefits against the risks of epoprostenol. We
6 knew that the drug could improve systems and
7 functional capacity, but we could not predict in an
8 individual patient whether such benefits would always
9 outweigh the ever present risk of a life threatening
10 event.

11 The acute onset of sepsis or stroke could
12 rapidly and unexpectedly change the risk to benefit
13 relation from one that was favorable to one that was
14 extremely detrimental to the patient.

15 Fortunately this is not the case with
16 treprostinil. Treprostinil produces clinically
17 meaningful effects without potentially life
18 threatening risks, and thus both patients and
19 physicians can weigh on an ongoing and individual
20 basis when severity of the infusion site pain against
21 the magnitude of improvement in symptoms.

22 As a result, physicians can feel

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 comfortable that treprostinil can be administered in
2 a way that insures that its benefits will outweigh its
3 risks of treatment in each patient who continues to
4 receive treprostinil treatment.

5 Such comfort is not possible if patients
6 are at an ongoing risk, a sudden, life threatening
7 event related to treatment.

8 Last slide.

9 In conclusion, the efficacy and safety
10 data that we have presented today supports the
11 proposition that treprostinil is indicated for the
12 treatment of symptoms in patients with pulmonary
13 arterial hypertension either of unknown etiology or
14 associated with intrinsic disorders of the pulmonary
15 vasculature.

16 Thank you.

17 CHAIRMAN BORER: Thank you very much, Dr.
18 Barst.

19 We'll take a few minutes here and then
20 deal with other questions we may have for you during
21 our discussion later, but, Tom, do you have some
22 questions you want to ask?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. FLEMING: Just a quick question.
2 We've seen in your presentation and also on page 136
3 in the FDA briefing document that on UT-15 the percent
4 that used opiates was 28 percent and anti-inflammatory
5 drugs 44 percent.

6 What were the corresponding percentages in
7 placebo, in the control arm vehicle?

8 DR. BARST: Do we have that data, Roger?

9 Dr. Jeffs said the use of narcotic
10 analgesics was less than -- I don't think that's
11 correct.

12 MS. STANDAERT: Please use the microphone.

13 DR. BARST: Dr. Jeffs said that the use of
14 narcotic analgesics for the treatment of infusion site
15 pain in the placebo group was less than one percent.
16 Narcotic analgesics were used in a higher frequency
17 for a number of these patients, particularly patients
18 with pulmonary hypertension associated with collagen
19 vascular disease. Because of other pain they not
20 uncommonly are treated with narcotic analgesics by
21 their rheumatologist.

22 I do not know if we have that exact data

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 number, but it was similar in both groups.

2 DR. FLEMING: If we could get it by the
3 break. My understanding from the FDA report is the
4 percentages that they gave was the percentage of
5 overall global use over the 12 weeks, and I would like
6 to know what the comparative percentages are. If it's
7 28 percent on intervention, what is it on control for
8 opiates? If it's 44 on anti-inflammatory, what is it
9 on control?

10 CHAIRMAN BORER: Yes, Steve.

11 DR. NISSEN: Yeah, I just had one sort of
12 brief comment. You know, you implied that the pain,
13 injection site pain, improves over time, but don't you
14 really mean to say that the reports decrease over
15 time? I mean, I think you can't really distinguish
16 those two from the data.

17 You know, you start patients with diabetes
18 on finger sticks, and at first they complain terribly
19 about having to stick their fingers every day, and
20 after a while they stop complaining about it. It
21 doesn't mean it doesn't hurt anymore. It just means
22 that they kind of give up on reporting it.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 So I think we probably ought to clarify
2 that a little bit.

3 DR. BARST: I think that's a very
4 important question. Obviously it's a subjective
5 response from the patients. When we see the patients
6 for follow-up we always ask about concern with regard
7 to pain, erythema, induration, and we do it on a
8 subjective scale.

9 And I certainly agree with what you're
10 saying. All I can say from an objective standpoint is
11 when we see the patients for follow-up, the degree of
12 erythema and frequently the degree of induration has
13 subsided over time with increasing duration of
14 exposure, as well as increasing dose.

15 CHAIRMAN BORER: Dr. Barst, you're an
16 expert in this area. I want sort of as a final
17 statement here before we take a little break your
18 opinion about something.

19 Many of the concerns with the intravenous
20 preparation with epoprostenol are mitigated by the
21 fact that there are some data suggesting improved
22 survival, albeit with small numbers of events, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 we're not sure it would hold up, but they're there and
2 have been generally accepted, I think, and yet we
3 didn't see that kind of natural history benefit from
4 these studies at least. Maybe it's there, but we
5 didn't see it.

6 So when we talk about the relation between
7 benefit and risk, we really have to understand. We
8 have to believe that there's a magnitude of benefit
9 that outweighs some of the risks that we have heard
10 about.

11 And when I look at the data, I understand,
12 and I think that Dr. Rich was absolutely right in
13 outlining for us the limitations of the unencouraged
14 six minute walk and Dr. Koch discussed the need to
15 think in another dimension as well, measurement of
16 symptoms by some other metric.

17 Nonetheless, the median increase in
18 walking distance was 16 meters. You walk the streets
19 of New York just like I do. So you know that until
20 you go north of 155th Street, 16 meters is less than
21 a quarter of a block.

22 What should we infer from a therapy that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 improves somebody's ability to walk less than a
2 quarter of a block? I mean, how meaningful is it?
3 How far can we extrapolate it?

4 DR. BARST: Maybe I could back up and go
5 through some of the points that you raised, and we'll
6 come to at least what my conclusion is based on my
7 experience.

8 One of the difficulties with assessing, as
9 we brought up before, the walk are the different
10 etiologies that we study, particularly including
11 patients with Eiseminger (phonetic), who have a very,
12 very slowly progressive course, as well as including
13 patients who are New York Heart Association Class II,
14 who are obviously less limited from an exercise
15 capacity standpoint.

16 To date, these patients have had no
17 effective therapy available for them if they are not
18 responsive acutely with vasodilator testing and can,
19 therefore, not be felt to improve with chronic calcium
20 channel blockade.

21 As Dr. Rich discussed, the natural history
22 of the pulmonary vascular disease in these three

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 groups, although variable, they all progress over
2 time, and there have been no reports of spontaneous
3 regression other than the one report that turned out
4 to be not regression.

5 Therefore, the sponsor elected to widen
6 the criteria to include patients that were less ill,
7 New York Heart Association Class II, who to date we
8 have felt do not warrant the risks which can be and
9 have been fatal using the only other approved therapy
10 we have, intravenous epoprostenol.

11 If we look at treating these patients
12 earlier in an attempt to avoid progression to Class
13 III and Class IV, in my opinion and in my experience,
14 this is a significant improvement to the treatment
15 armamentarium that we have for these patients.

16 Number two, when we looked at the survival
17 curves that Dr. Rich showed for patients who
18 discontinued due to adverse events, infusion site pain
19 versus those who discontinued due to deterioration, I
20 believe that we were able to identify patients if they
21 discontinued due to adverse events, that they were
22 less ill and they subsequently could be treated with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 an effective therapy.

2 As I discussed at the very end, it's very
3 difficult when the risks can be titrated, which is
4 what we have with treprostinil. If we have
5 significant risks, we can manage them; we can adjust
6 them. We've never had any fatalities, any
7 catastrophic events, which is not the case with IV
8 epoprostenol.

9 And unfortunately, in our experience at
10 our center, which is with more than 300 patients with
11 intravenous epoprostenol, we have had patients who
12 have had significant clinical improvement, and then
13 they developed a fatal episode of sepsis.

14 CHAIRMAN BORER: Okay. Well, that's a
15 nice summary, and I think it carries much weight
16 because you see a lot of these people. So your
17 opinion is meaningful.

18 Well, thank you very much.

19 We'll take a ten minute break, but before
20 we do, I've been asked to do one other thing. It may
21 say 15 minutes. I'm telling you it's ten minutes,
22 after which, at 11:15 sharp, we'll have some formal

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 comments from Dr. Temple.

2 The FDA has requested that the members of
3 the committee should be introduced, and so I'll do
4 that starting from the left end.

5 Dr. Alan Hirsch, who is Associate
6 Professor of Medicine and Radiology at Minnesota
7 Vascular Diseases Center at the University of
8 Minnesota.

9 Paul Armstrong, Professor of Medicine,
10 University of Alberta.

11 JoAnn Lindenfeld, Professor of Medicine in
12 the Division of Cardiology at the University of
13 Colorado Health Science Center.

14 Tom Fleming, Dr. Tom Fleming, professor
15 and chair of the Department of Biostatistics at the
16 University of Washington.

17 My name is Jeff Borer. I'm the Gladison
18 Roland Harriman Professor of Cardiovascular Medicine
19 and Chief of the Division of Cardiovascular
20 Pathophysiology at Cornell.

21 Next to me is Dr. -- oh, here we are --
22 Dr. Andrew Brem, Division of Pediatric Nephrology at

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the Rhode Island Hospital.

2 Next to him -- and Dr. Brem is a temporary
3 voting member. Everybody else I've introduced is a
4 permanent member of the committee, as is Dr. Steven
5 Nissen, who's the Vice Chairman of the Department of
6 Cardiology and Professor of Medicine at Ohio State,
7 working at the Cleveland Clinic.

8 Next to him is Gloria Anderson, Dr. Gloria
9 Anderson is the Fuller F. Calloway Professor of
10 Chemistry at Morris Brown College, and she is the
11 consumer nominated representative to the committee,
12 also a temporary voting member.

13 And next to her is Dr. Michael Artman,
14 Professor of Pediatrics and Pediatric Cardiology at
15 New York University Medical Center.

16 There's one temporary voting member who is
17 not yet here, but I assume will be here for the
18 afternoon, and that's Dr. Jeffery Kopp, the Kidney
19 Diseases Section of the National Institute of Diabetes
20 and Disease of the Kidney at the NIH.

21 We'll now take a break. I think I took a
22 couple more minutes. So you only have seven minutes

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 until 11:15.

2 (Whereupon, the foregoing matter went off
3 the record at 11:06 a.m. and went back on
4 the record at 11:16 a.m.)

5 CHAIRMAN BORER: Okay. We'll get started
6 again with some formal comments about the regulatory
7 considerations revolving around NDA 21-272 by Dr.
8 Temple, the Director of Office of Drug Evaluation I.

9 DR. LIPICKY: Jeff, as Dr. Temple is going
10 to the podium, I want to just -- pertinent to the
11 question you asked before the break, this was a feel
12 good kind of development program. We knew that there
13 would be insufficient morbidity and mortality data,
14 and it was can people feel good, and then you sort of
15 have ambiguous amounts of morbidity and mortality
16 data.

17 That's our fault. We didn't ask for it,
18 but it is what the data is.

19 CHAIRMAN BORER: I wasn't placing a value
20 judgment on it. I just wanted an opinion.

21 DR. LIPICKY: Well, I just wanted to place
22 the blame.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN BORER: Okay. Bob.

2 DR. TEMPLE: You might be puzzled why I'm
3 even talking. It's common for cardiorenal and its
4 associated people not to present but only to ask
5 questions.

6 The reason we thought it might be a good
7 idea was that if you've read all of the review, and I
8 don't know if they got Ray's review or not, but if you
9 read all of the reviews, they all say no, and we,
10 therefore, thought it was important to communicate the
11 idea that we are listening and that this is being
12 presented for a reason.

13 Usually you don't have quite as consistent
14 a set of views.

15 As you've seen from the material provided
16 you, the Cardiorenal Division reviewers and
17 supervisors have pretty consistently reached the
18 conclusion that treprostnil shouldn't be approved for
19 pulmonary hypertension.

20 That doesn't mean everybody thinks this is
21 open and shut, and that's why we're here. It's
22 obvious from the questions that members of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 committee have already been raising that you already
2 appreciate a good deal of what I'm about to say. In
3 fact, if I were more competent at making slides, I
4 would have adjusted them to take that into account,
5 but I'm a little challenged on those matters.

6 Am I pushing the right button?

7 Despite the negative conclusions, all of
8 the reviewers have found that the decision is a very
9 close call. The disease is plainly a bad and
10 progressive one. The available treatment is onerous
11 and difficult to use, although it may, in fact, have
12 a survival effect, which certainly needs to be taken
13 into account.

14 Potential alternatives, one of which
15 you'll see tomorrow are not serious risk free, and an
16 important question is in that situation how much
17 weight should be given to a noxious but not dangerous
18 symptom, notably injection site pain that the patient
19 can presumably assess by herself.

20 That, of course, has to be viewed in light
21 of the nature of the benefit, and such matters as the
22 fact that most of the patients treated in the trials

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 go on and stay on therapy certainly is something that
2 one might consider.

3 The effect on the primary endpoint plainly
4 failed to meet the prespecified statistical criteria,
5 as everyone has acknowledged, but it is close, and the
6 question is, of course, is very close good enough and
7 what are the implications for this and other
8 applications if one concludes that it is.

9 A question that always arises in such
10 cases, whether other findings could buttress the
11 result and, you know, what, for example, is the role
12 of a principal supporting endpoint, not a well defined
13 concept.

14 And of course, even if you believed the
15 whole matter is the magnitude of the effect seen a
16 meaningful benefit, both considered alone and as the
17 sponsor has urged together with the other effects that
18 are related to it?

19 There's a very complex question, perhaps
20 impenetrable, but in any event, hard to answer, is
21 whether the analysis of the six minute walk, given the
22 dropouts and the potential for informative censoring,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 are really valid or falsely favorable so that the
2 small effect is even smaller or perhaps even
3 nonexistent.

4 The other findings related to benefit, the
5 symptomatic benefits, are generally quite favorable;
6 one might even say very favorable, but with one
7 exception, notably the Borg score. They are
8 potentially contaminated by unblinding of the
9 investigator because the injection site pain makes it
10 fairly obvious at least in most cases who's on the
11 drug.

12 Even the Borg and exercise test could be
13 presumably unblinded for the patient, and that, too,
14 could have implications.

15 The sponsor has suggested that some of the
16 symptom effects could be persuasive anyway. For
17 example, the new appearance of a problem might not be
18 so susceptible to placebo reporting effects.

19 And then, of course, there are multiple
20 different symptoms that have been looked at, and the
21 question always is: is multiplicity a problem?

22 A question raised by the medical review is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 what the increasing dose means, that is, is it
2 disturbing evidence of tolerance to whatever effect
3 the drug has or, alternatively -- and in this case I
4 have to say this is what my view is -- an inevitable
5 consequence of a design that allowed dose increases if
6 patients were still symptomatic, which of course,
7 almost all were and would be expected to be despite
8 treatment.

9 It seems worth noting that the increase in
10 dose on placebo was about twice that of treprostnil,
11 and I guess one could wonder whether that is some
12 further suggestion of a benefit.

13 The whole thing also makes me wonder
14 whether an adequate dose was achieved in the course of
15 the study, and of course, the study was not designed
16 to look specifically at dose response. If one wanted
17 to do that, one would randomize to fixed final doses
18 even if you titrated along the way.

19 As you've heard, the primary endpoint was
20 the six minute walk. It was hoped that a nominal
21 significance of .049 would be achieved in both studies
22 or at least in one study and .01 on the pooled data.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 What was observed was short of that for
2 the individual studies, but close and somewhat better
3 for the combined result.

4 One of the things that we always like to
5 say is that we're not the slave of p values, but in
6 the event they often seem pretty important. So what
7 we have here is two studies that are quite close to
8 their goal analyzed together having a moderately
9 extreme result, although not as extreme as the .00125
10 we like to see when there's a single study, and the
11 question is: is this result convincing statistically
12 at all? And, second, does the effect seem clinically
13 meaningful by itself or together with the other data
14 as the sponsor has urged you to believe?

15 A critical question goes to whether there
16 is an effect at all on the primary endpoint, which is
17 very important to even thinking about all the other
18 matters, is the possibility of informative censoring
19 in the analysis.

20 Now, the medical review notes that many
21 patients on treprostiniil dropped out of the study and
22 that there was an inherent bias because these patients

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 could never get a low value in the analysis even if
2 they did badly, for example, died later.

3 In the planned analysis, discontinuations
4 because of death, deterioration or transplant got the
5 lowest rank, and everybody else who dropped out for an
6 adverse event got the last observation carried
7 forward, which was not always very close in time to
8 the dropout.

9 Now, I don't believe it's correct to say
10 that the dropouts mean that the procedure must be
11 biased. It is true that it might be biased. And I'm
12 going to try to explain in my nonstatistical way what
13 informative censoring is, and Tom can tell me how
14 wrong I am.

15 This procedure is biased only if it
16 removes patients who are worse than the remaining
17 patients and worse in a way that isn't reflected in
18 the exercise test that is used to score them. Then,
19 indeed, the censoring would be informative.

20 Now, could that be true? Well, the answer
21 is, of course it could. Discontinuation for a nominal
22 adverse reaction could be at least in part related to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 how well people are doing. That is, they could drop
2 out for pain only because they aren't doing that much
3 on the exercise test so that there could be a bias in
4 deciding who with an adverse reaction decides to leave
5 the study.

6 If this were not reflected in the last
7 observation used in the analysis either because it was
8 obtained earlier and a contemporary exercise test
9 might have revealed such deterioration, it could also
10 be because doing badly isn't reflected in the exercise
11 test. There may be some intuitive sense that things
12 aren't going well.

13 But in either case then censoring at the
14 time of dropouts would be informative and would lead
15 to an unequivocal bias.

16 It's pretty obvious given the closeness of
17 the result that even a small amount of this would be
18 a problem, and I don't believe this problem is
19 entirely resolved by the analysis the sponsor
20 presented showing that the dropouts due to pain are
21 nothing like the people who discontinued because of
22 deterioration. That is plainly true and would be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 expected, but they still could be worse than the other
2 people in the trial anyway, even if they weren't as
3 bad as someone who dropped out for obvious
4 deteriorations. So that's not easy to come to grips
5 with, perhaps never can be answered definitively.

6 The review shows that assigning a low rank
7 to selected withdrawals, that is, three kinds, those
8 who died or were terminated in less than 100 days,
9 those who received Flolan within one month of
10 discontinuation, and those who ever received Flolan
11 eliminated statistical significance for the most part
12 at the levels we saw.

13 I gather from some of the discussion
14 Jeffrey had with the sponsor that a lot of that
15 depends on what you do with each patient, but it
16 certainly gets it well below the prespecified levels,
17 but then you might expect it to do that, and those
18 analyses are appropriate only if, in fact, censoring
19 was informative, and it's just very hard to know.

20 It's perfectly possible that the withdrawn
21 patients, even the ones who eventually died, were, in
22 fact a random sample of the group or were adequately

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 located in the non-parametric analysis by their last
2 observation. Very hard. I'm glad you have to answer
3 that.

4 Now, another question also discussed at
5 considerable length is whether the original endpoint
6 can be buttressed by these other endpoints. It's
7 obvious that exercise tolerance or exercise testing
8 wasn't all one hoped it to be. It's not an
9 unreasonable endpoint, but the ways in which it was
10 not perfect were not fully anticipated because if they
11 had been, then the chosen endpoint would have been a
12 combined endpoint in the first place.

13 It seems fairly clear that people with
14 relatively preserved exercise, say, over 300 meters,
15 don't improve much, and it's been suggested that's
16 because their major limit isn't dyspnea. An
17 implication of this is one should give more
18 credibility to the low baseline group, which, in
19 general, did better.

20 And the second possibility is that people
21 don't exercise to real exhaustion, which is sort of
22 obvious from the Borgs, or led to some other point,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 which is something like how fast they want to walk.

2 And then again, an implication strongly
3 supported by the sponsor is that one should look at
4 both exercise test and the Borg score. If one wants
5 to do that, it seems to me that's a far more credible
6 thing. If you believe the exercise test, albeit
7 marginal, is plausible, then sort of it's okay to
8 noodle around with other things. If that failed, then
9 there would be some real question about how much you
10 should do that.

11 So you've seen the combined result. It's
12 statistically robust and is immune to the various ways
13 of handling the dropouts that we proposed before, but
14 it is inevitably after the fact, after it's Ohm
15 metered from that slide.

16 After the fact doesn't mean it's out of
17 the blue. The Borg score was considered an important
18 endpoint, albeit not the primary endpoint.

19 I should note that our statistical
20 reviewer didn't much like the idea of combining them,
21 but thought if you want to look at the Borg score a
22 lot and pay attention to it, that was okay, but it

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 should stand on its own merits even though it wasn't
2 the primary endpoint.

3 So the fundamental question here is
4 whether the combined analysis is really a finding or
5 really a hypothesis.

6 Obviously we as the agency and this
7 committee has a long history of skepticism regarding
8 these kinds of adaptive analyses because, as we know,
9 all subgroup analyses and all later analyses always
10 seem intelligent. Nobody presents stupid ones to us.

11 That doesn't mean they aren't the play of
12 chance. So it's a very thorny question. We would
13 certainly never say you can never do that. The
14 question is when and how plausible it has to seem.

15 Similarly, we're skeptical about looking
16 at subsets, say, the low baseline group here as a way
17 to conclude there's an effect, but if the overall
18 result is positive, which is, of course, something
19 we're debating here, there may be some legitimacy to
20 looking among various subsets to see if you can learn
21 something.

22 And any time you say that, you have to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 point out the PEDO (phonetic) analyses of Zodiacal
2 signs and things like that to remind you of how
3 dangerous it is to even think about such things. In
4 that sort of case, consistency of the subset finding
5 in the two studies would be helpful.

6 Finally, it's worth coming to symptoms.
7 One has to be troubled by the fact that we have
8 largely dismissed the analysis of symptoms because
9 we're worried about unblinding. It's perfectly
10 reasonable to be worried about blinding, but does that
11 mean there's no way ever to work up a drug that has an
12 only symptomatic effect if unblinding is inevitable?

13 I mean, if you're asking patients a
14 question about symptoms and they're inevitably
15 unblinded, does that mean there's no way? That's a
16 disturbing conclusion, but it is nonetheless
17 troubling.

18 It's worth pointing out that on many of
19 the symptom measures, the composite scores, the Borg
20 score, the dyspnea-fatigue analysis, the results are
21 quite extreme, and so an important question is how
22 totally one needs to dismiss findings like that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 because of the potential for unblinding.

2 You've heard the sponsor argue that in
3 some cases it's not obvious that unblinding would be
4 a problem, for example, if people newly develop a
5 symptom they didn't have at baseline. Is it
6 unblinding that would make them more likely to do that
7 on placebo than on drug?

8 Part of thinking about that is to look at
9 how much selection among the various symptoms there
10 has been, but in this case I think it's fair to say
11 they all seem to lean in the same direction, and it
12 could be at least argued that the ones that have been
13 selected for emphasis like syncope have been chosen
14 because they're more plausibly not affected by
15 unblinding.

16 Anyway, that's my summary of the issues.
17 It's obvious that you're already aware of all of these
18 things, and I'll look forward to the discussion.

19 CHAIRMAN BORER: Before we move on to Tom
20 Fleming's review for the committee, there are a couple
21 of questions that Dr. Armstrong wants to raise that we
22 should have resolved before we get into our

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 discussion, and Dr. Barst wanted to make one point
2 about the natural history effects.

3 And why don't we take a couple of minutes
4 for that? First, Paul.

5 DR. ARMSTRONG: I had two questions on the
6 safety issue. The first was what was the median dose
7 that led to the withdrawal? And how did that compare
8 with the median dose in the patients who remained in
9 the study?

10 I saw the dose response for side effects,
11 but not the median dose at the time of withdrawal due
12 to adverse effects.

13 And the second question was: were there
14 any defining or special characteristics of the
15 patients who were forced to withdraw as opposed to
16 those that continued in the study as one looked at
17 their baseline characteristics or other features?

18 CHAIRMAN BORER: Can we have the
19 microphone on please over there?

20 DR. BARST: Those are two very important
21 questions. The median dose for the 18 patients in the
22 treprostini1 treated group who withdrew because of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 site pain was 2.5 nanograms per kilogram per minute,
2 very consistent with what we showed when the onset of
3 pain was most patients had their most significant
4 onset of pain early with the low dose. It wasn't due
5 to incremental increases.

6 And the second point is as far as I'm
7 aware, we did not -- and I don't think we have
8 specific data -- but as far as I'm aware from patients
9 that we had that dropped out, there was no evidence
10 that they were any different from their baseline
11 demographics, hemodynamics or exercise studies.

12 The two points I wanted to raise very
13 quickly were two points that Dr. Borer asked in his
14 question, which I didn't answer either of them.

15 Could I have the slide?

16 One was with regard to the question of
17 survival benefit with intravenous epoprostenol and
18 that we did not see a survival benefit with
19 treprostinil even though the study wasn't powered to
20 look for that.

21 There have been two randomized clinical
22 trials evaluating the effects of epoprostenol. Both

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 of them were open label, and they were not placebo
2 controlled. The first one was with primary pulmonary
3 hypertension patients, which was a 12 week study, and
4 in the placebo group eight patients did die during the
5 12 weeks and no patients died in the epoprostenol
6 group.

7 It's a very small number of events, and
8 this often can be misleading. And other trials that
9 have initially suggested there was a survival benefit
10 with subsequent larger trials, the survival benefit
11 was no longer there. So this certainly raises a
12 possibility, but my belief is that this is a very
13 small number of events.

14 The second randomized trial, again, an
15 open label trial was subsequently carried out with
16 patients who had severe pulmonary hypertension
17 associated with a scleroderma spectrum of disease. In
18 this study, which was 111 patients, there was no
19 evidence of a survival benefit.

20 My interpretation of these studies is
21 really based on the small number of events, that these
22 do not demonstrate in a very robust manner that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 there's a survival benefit during the clinical trials
2 with intravenous epoprostenol.

3 The two other points that were asked that
4 I did not address, one was the clinical meaningfulness
5 of the endpoints that we looked at, and when I was
6 asked about walking 16 meters, is that a clinically
7 meaningful improvement?

8 I certainly agree if every patient in the
9 study only improved 16 meters and we didn't look at
10 the totality of any of the other endpoints from a
11 symptomatic improvement, that would not be very
12 clinically meaningful.

13 But certainly there was a range of
14 improvement with some patients walking much farther
15 than the 16 meters, in addition, with significant
16 improvements in all the other signs and symptoms that
17 we looked at.

18 And lastly, although we did do it as a
19 post hoc analysis and our prespecified endpoint only
20 included treatment failure as defined by death,
21 transplant, or worsening requiring intravenous rescue,
22 when we did take into consideration patients who

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 significantly worsened requiring hospitalizations, as
2 well as those patients who significantly worsened and,
3 therefore, were unable to walk at completion of the
4 trial, it is very suggestive that there was
5 significant difference from that standpoint in the
6 treprostini treated group.

7 Thank you.

8 CHAIRMAN BORER: Thank you.

9 JoAnn, did you have one?

10 DR. LINDENFELD: Dr. Barst, let me just
11 come back to this issue of withdrawal. You said that,
12 or at least I think you said, that virtually no
13 problems have been seen with withdrawal. So I had two
14 questions. The first is maybe you could briefly
15 summarize what data we have observing patients during
16 withdrawal, and the second is I think that withdrawal
17 is a problem with other agents used in pulmonary
18 hypertension calcium blockers in epoprostenol.

19 So if there isn't a withdrawal problem,
20 could you tell us why you think there isn't with this
21 specific drug?

22 DR. BARST: Those are very good points you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 raise. In the 18 patients who withdrew during the 12
2 week trial, there were no clinically significant from
3 a pulmonary hypertension standpoint side effects with
4 withdrawal. I believe and in my experience that was
5 based on exceedingly low doses at the time that we
6 withdrew the medication.

7 In addition though, even though the
8 patients were at very low doses, the majority of the
9 patients were weaned, and they were not abruptly
10 stopped.

11 Based on the significantly longer half
12 live of subcutaneous treprostinil compared to
13 intravenous epoprostenol with stopping, and
14 particularly with weaning, we have not had any serious
15 adverse events.

16 I think you asked another question.

17 DR. LIPICKY: That means you don't know
18 whether there is a problem or not. Isn't that what
19 you just said?

20 DR. BARST: Yes.

21 DR. LIPICKY: Okay.

22 DR. LINDENFELD: I think you answered my

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 question at least partly. There do appear to be
2 withdrawal problems with other drugs. Calcium
3 blockers do have a longer half-life. So one might ask
4 -- I'm not asking directly, but one might ask if
5 there's no withdrawal, is there an effect.

6 DR. BARST: Okay. That's also a very good
7 point, and that's what I wanted to bring up before Dr.
8 Lipicky asked me his question.

9 In the open label study, we do have a
10 significant -- we do have a number of other patients
11 who withdrew. Either they were weaned or it was
12 abruptly stopped, and if we look at those patients, in
13 addition to patients in whom they had delivery
14 problems from pump malfunction, there are a number of
15 patients in whom their pulmonary hypertension symptoms
16 increased, such as dyspnea, but there were no
17 catastrophic events with weaning or discontinuation,
18 which is what we have seen with epoprostenol.

19 In my opinion and my experience, that is
20 very consistent with it. There was an effect as
21 opposed to no effect from the treprostinil.

22

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. LINDENFELD: Just one other question
2 I asked earlier, and we waited until your
3 presentation. I'm concerned with the large number of
4 patients on pain medications. We don't know exactly
5 how many were on pain medications at the time the 12
6 week exercise test was done, but do we have any data
7 at all about how taking those pain medications
8 influences exercise capacity or influences the
9 judgment about symptoms?

10 DR. BARST: Yes, we do.

11 Can we have -- I don't know the number of
12 the slide.

13 We have a slide that looked at was there
14 an interaction between patients who had been
15 prescribed opioids during the clinical trial and those
16 who had not and was there an interaction with their
17 exercise response as well as their symptoms of Borg
18 and dyspnea.

19 DR. KOPP: While you're bringing that up,
20 I'd ask the same question not just for opioids which
21 we focused on, but even non-steroidal or Tylenol use.
22 In other words, all analgesics are approved because

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 they have effects in the CNS, which could affect
2 exercise time.

3 DR. BARST: Absolutely. On the slide that
4 discusses the interaction with regard to narcotics, it
5 also includes whether there was an interaction with
6 non-steroidals.

7 I do not think we have Tylenol on that,
8 but I'm going to turn it over to Dr. Koch.

9 DR. KOCH: Basically this display shows
10 statistical assessments of interaction with respect to
11 these different patterns of medication. More simply,
12 they address the question of whether or not treatment
13 differences have a tendency to be somewhat bigger for
14 those using such a medication versus those who did
15 not.

16 Stars appear relative to a p value that
17 would be less than .20. so that's why you see some
18 larger p values with stars, as well as some smaller
19 ones.

20 As the footnote indicates, a star is
21 associated with a smaller treatment effect, and there
22 would have been a different symbol had it been

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 associated with a larger treatment effect. The only
2 designating symbols that you see are single stars,
3 which basically means that when there is some
4 suggestion of an interaction, it is associated with a
5 smaller treatment effect among the users, not a larger
6 treatment effect.

7 So to whatever extent this other
8 medication was used, it did not lead to an increase in
9 a treatment difference. Although this is an
10 exploratory analysis, these are based on post baseline
11 criteria, but they basically indicate that support for
12 whatever differences were seen came more from those
13 not using the concomitant medication than necessarily
14 from those using it.

15 But these kinds of assessments are very
16 hard to interpret statistically because you're
17 integrating a post baseline assessment in with it.

18 CHAIRMAN BORER: Tom did you want to ask
19 a question about the frequency of opioids?

20 DR. FLEMING: Yeah. We were going to be
21 provided -- if we look at use of opioids and anti-
22 inflammatory drugs, it was 28 and 44 percent

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 respectively in the intervention group. What were the
2 rates on the control?

3 DR. JEFFS: We don't have a slice for
4 this, but in the treprostinil group, 44 percent of the
5 patients used opioids at any time for any reason, and
6 this was prescription. What I'm going to quote you is
7 prescription rates. For placebo, it was 53 patients
8 or 22 percent, and for the non-steroidal, anti-
9 inflammatory drugs it was 22 percent of patients in
10 the treprostinil group and five percent of patients in
11 the placebo arm.

12 DR. FLEMING: The FDA reports 44 percent
13 with anti-inflammatory drugs. You're indicating an
14 increase from five to 22. They said they were 44.

15 DR. JEFFS: Our data, and we've just
16 checked our database, suggest that there's 22 percent.

17 DR. FLEMING: All right. Let's go on.

18 CHAIRMAN BORER: Okay. The reviewer for
19 the committee is Tom Fleming.

20 Tom, can you present your review?

21 DR. FLEMING: Thanks, Jeff.

22 Yes, let me go ahead, and I'll overlap

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 somewhat with Bob Temple and may be elaborate on a few
2 of the key issues he's made and try to provide a
3 quick, global summary.

4 My focus always in looking first at
5 efficacy and then safety, my focus always in efficacy
6 is guided by what the analysis, plan and sponsor and
7 FDA had targeted as the objective of the trial, which
8 was, in fact, the six minute walk.

9 And the protocol was designed specifically
10 targeting a 55 meter difference. The actual global
11 pooled estimate showed a ten meter difference, and as
12 has already been probed pretty extensively by the
13 committee, this raises a lot of significant issues
14 about whether even if we could conclude this is
15 significantly established, is this clinically
16 meaningful?

17 It certainly is a far more modest level of
18 improvement than had been targeted by the sponsor's
19 own sample size calculations in the analysis plan.

20 Turning to the issue of statistical
21 significance, the significance levels did not meet the
22 target for strength of evidence established for the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 individual studies at 05 or for the pooled analysis at
2 01.

3 The issues are complicated though as we've
4 already heard today by the complexities of the number
5 of dropouts. There were essentially, I think, 16
6 versus 33 dropouts from intervention on control and
7 UT-15, respectively.

8 Without question though, I think the FDA
9 has put forward at a minimum a recognition that if
10 someone dropped out and within the 100 days died or
11 had a transplantation or had worsening disease, it's
12 extraordinarily reasonable to give that person the
13 worse score, and I think that's unequivocally an
14 appropriate conclusion, and if you simply make that
15 adjustment, the significance level in the pooled
16 analysis is on the order of .015 to .02. So clearly
17 it didn't even hit the 01.

18 But I'm a bit troubled to go beyond that
19 and just take a couple more moments. The
20 discontinuation rates due to AEs were one versus 18,
21 and the question is: is there, in fact, further
22 informative censoring or bias induced by a last

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 observation carry forward analysis beyond simply
2 addressing the scores you're giving to the deaths,
3 transplantations, or discontinuation for worsening
4 disease.

5 Bob raised one of the issues of concern
6 with missing information and censoring, and he's right
7 about that, and that is: is censoring informative?
8 Specifically, are these people who are dropping out
9 for AEs any different or any likely to be worse off
10 than those people who remain?

11 Because in censoring them, essentially the
12 assumption as Bob correctly pointed out that we're
13 making is that if people are dropping out for AEs, we
14 can censor them and essentially represent the results
15 best by those people who continue to be followed.

16 The sponsor gave one analysis to try to
17 address this, and they used probability of going on
18 Flolan for those who discontinued for AEs, and they
19 compared it to those who discontinued for worsening
20 disease and said that because those who discontinue
21 for worsening disease by 100 days at 75 percent chance
22 of going on Flolan, only 50 percent chance for those

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 who were discontinuing for AEs, this is a good result.

2 My thought is that's not the comparison I
3 want. I want to know whether those who were
4 discontinuing for AEs were worse off than the people
5 who didn't discontinue, and having a 50 percent chance
6 of going on Flolan is, in fact, not a good thing.

7 And, in fact, when the FDA did a second
8 and third analysis to provide various adjustments for
9 that, the global p values were on the order of .1, and
10 the individual study p values were on the order of .2.

11 But that's not the whole story yet.
12 There's still another aspect of this, and that is look
13 at the nature of the effect that we see on six minute
14 walk. What we see at 12 weeks is essentially a ten
15 meter improvement.

16 By one week it was already 11 meters.
17 Interesting that in the intervention group, in spite
18 of the low dose and short term, you achieved all of
19 the effect in the intervention group in the first
20 week.

21 Well, but then you look at the placebo and
22 find that the placebo has the same effect. The

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 placebo basically has an eight meter improvement in
2 that first week. So maybe there's some kind of a
3 regression to the mean phenomenon going on here.

4 The issue is when you look at the effect
5 pattern for week one versus week 12, what's apparent
6 is that there's this full increase in both placebo and
7 intervention at week one. The difference in treatment
8 really emerges as you see that the intervention group
9 has no change then through 12 weeks, while the placebo
10 drops back to zero.

11 Well, think about this. How could you
12 achieve this effect with an inert agent? Well,
13 essentially if by week one you already see the
14 increase to ten meters, how do you keep that at ten
15 meters?

16 You censor everybody and use last
17 observation carry forward, and it's still going to be
18 ten meters. So the second key issue, Bob, for last
19 observation carry forward is not only am I confident
20 that there is not informative missingness. I have to
21 be confident that there isn't a natural history change
22 over time.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 This treatment effect entirely occurred
2 when the placebo dropped over time and the
3 intervention group didn't, and so these 18 people, 18
4 versus one, these AEs that I'm censoring in the
5 intervention group, all get the good graces of staying
6 constant over time, which is exactly where the
7 treatment effect is coming from.

8 So my sense is that there are certainly a
9 combination of significant issues that the FDA has
10 recognized in their reviews. This difference from a
11 clinical perspective is clearly much more modest than
12 had been targeted in the protocol.

13 I think it's also controversial to say
14 that the statistical significance is borderline. It
15 clearly didn't hit the target. It's controversial to
16 say whether it's even close to the target when you
17 make proper adjustments for the missingness bias that
18 is clearly differentially larger in the intervention
19 group.

20 Let me move on now and quickly touch on
21 some of the key secondary measures.

22 The analysis plan had indicated in Section

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 921 that six minute walk was the primary endpoint.
2 Their target in Section 922 is to go on to what they
3 call principal reinforcing endpoints, and here is
4 where, as we've seen today, I think some of the most
5 encouraging evidence occurs, although it's not
6 uniformly encouraging.

7 They had three specific measures listed as
8 principal reinforcing endpoints. One of these is the
9 dyspnea-fatigue rating, and essentially what we see,
10 as was interpreted by the FDA, is that there is a
11 difference here. It is nominally quite significant.

12 From an interpretation perspective, what
13 it amounts to is essentially comparable to what you
14 would have if one third of the patients had a one unit
15 increase in each of the three components, the pace,
16 the task, and the functional impairment.

17 So I think there is considerable
18 statistical evidence of a difference there. It seems
19 though to be fairly modest on a clinical spectrum.

20 The second of three endpoints was looking
21 at the 16 signs and symptoms and categorizing them as
22 minus one if it worsens; zero, no change; or plus one

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 if it improved. Conceivably the range of scores for
2 a patient could go from minus 16 to plus 16.

3 I looked on page 124 and counted up all of
4 those that showed improvements and worsening, and on
5 the placebo arm, there were comparable numbers of
6 improved and worsened, not a meaningful change over
7 time.

8 On the UT-15 arm, there were more that
9 showed improved than worsened, but on average, the
10 average patient had roughly a half to two thirds more
11 improved than worsened of these 16. So, again, we see
12 what is certainly, I think some statistically strong
13 evidence, but the issue is is it clinically strong
14 effects.

15 There are other issues here interpreting
16 the strength of evidence. I won't go into great
17 lengths on them, but we did have a lot of missingness
18 and there are the issues of unblinding.

19 The analyses that are put forward by the
20 sponsor to address whether there's bias due to
21 unblinding don't address the issue. It's not that I
22 believe they put forward the wrong analyses. There

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 just aren't the kinds of analyses that you would
2 really need to do. It's not possible to definitively
3 establish whether or not blinding had any effect.

4 But I would be persuaded to support the
5 conclusion that it's unlikely that the unblinding
6 accounted for the full effect that was seen.

7 The missingness though is an additional
8 issue. There were 52 people that weren't included in
9 those analyses, and they were differentially higher in
10 the intervention arm, and those worry a statistician.

11 So I think there are concerns about the
12 strength of the statistical conclusions because of the
13 likely unblinding and because of the missingness,
14 although my sense is that in likelihood they don't
15 account fully for the effects.

16 Let's go to a tertiary level. Section 923
17 in the analysis plan is the first place you see the
18 Borg dyspnea score. There seems to have been some
19 strong arguments that this is focal. It's curious to
20 me that it doesn't show up until the tertiary level in
21 the analysis plan.

22 If you look at the Borg dyspnea score,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 like the symptoms and dyspnea fatigue rating, you see
2 evidence of some difference, on a ten point scale and
3 0.8 unit difference.

4 On the other hand, when you look at the
5 Minnesota Living with Heart Failure questionnaire, on
6 the global physical dimensions and emotional
7 dimensions in either study, they're all non-
8 significant, although if you pool, you get a
9 significant result on physical dimension.

10 My sense is overall here, you put all of
11 this together, and there certainly is some evidence of
12 effects on symptoms. It's modest, and it's perplexing
13 if the Borg is such an obvious measure why it was
14 tertiary in the analysis plan.

15 The third that I've skipped over, the
16 third of the principal reinforcing endpoints I've
17 skipped over because I want to focus on a bit, and
18 that is certainly for these patients I would
19 anticipate that one of what the sponsor did address as
20 one of the three principal reinforcing endpoints I
21 would think would be critical, and that is was there
22 a difference in survival. Was there a difference in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 transplantation? Was there a difference in
2 discontinuation due to clinical deterioration? Was
3 there a difference in press or support of Flolan?

4 Respectively on each of these, there's not
5 only not a significant difference; there's not a hint
6 of a difference. Basically deaths are ten to nine;
7 transplantation, one to zero; discontinuation due to
8 clinical deterioration, six versus six; requiring
9 press or support of Flolan is 13 versus 12.

10 Sponsor's view, well, here was evidence
11 that we weren't harming people, but I thought the
12 intention here was to actually provide clinical
13 benefit, and are these not the major sequelae of
14 pulmonary arterial hypertension, and should we not
15 have at least hoped to have seen something?

16 Well, by the analysis plan, it was, in
17 fact, I think, hoped that we would see something. It
18 was in there as one of the principal reinforcing
19 endpoints.

20 On the safety side, the sponsor has
21 certainly noted that there are substantial issues that
22 arise with pain, injection site pain. If we look at

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 serious AEs, it's 39 percent versus two percent;
2 injection site reaction, 38 percent versus one
3 percent; use of opiates, anti-inflammatory drugs,
4 they're all very substantially increased.

5 And what I struggle with is trying to sort
6 out given that essentially we have no evidence of
7 effects on major sequelae of pulmonary arterial
8 hypertension, we have suggestions on secondary
9 measures of some benefits on symptoms that by my sense
10 appear modest, but on the other hand, we have these
11 very significant issues relating to pain and
12 essentially how does one weigh those modest benefits
13 on symptoms against these issues in pain that are
14 sufficiently significant to really increase
15 substantially use of opiates?

16 So I think as I try to kind of pull this
17 together and summarize, I think from an efficacy
18 perspective I'm drawn heavily by what it was that we
19 said we were supposed to do in this trial, which was
20 establish an effect on six minute walk. The overall
21 established effects are very modest, and I think
22 statistically not only don't achieve significance, but

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 I think it's controversial as to whether they are
2 viewed as close to significant.

3 Flolan, when it was a 45 meter
4 improvement, the target was 55. We achieved ten. At
5 one point it was stated, well, maybe we didn't have
6 the right population. Maybe we didn't look at PPH,
7 and yet when we looked in the subgroup of those with
8 primary pulmonary hypertension, the effects were still
9 only about 13 meters. So they weren't strikingly
10 different.

11 And there are as I've mentioned these
12 potential biases that we have due to informative
13 censoring and unblinding.

14 The subgroup, it's an interesting issue in
15 the subgroup, that you see those that start off with
16 shorter six minute walks potentially showing more
17 benefit, but at best that really would need to be
18 confirmed in an independent trial.

19 When we look at the more significant
20 effects of major sequelae, Flolan, eight versus zero,
21 we just heard an extension of that in the scleroderma
22 population. Overall though it's still 13 percent

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 versus four percent, including the scleroderma
2 population.

3 Probably not compelling proof, but
4 certainly a strong suggestion that Flolan can
5 influence mortality. We didn't see that here. We saw
6 essentially no difference.

7 I'm wondering if we should have looked
8 over a longer time. It may well be. We hear
9 testimonials. I'm always very concerned about
10 interpreting testimonials because we didn't hear from
11 a lot of people, but there is, in fact, certainly
12 always the possibility that over a longer period of
13 time we might have seen a different benefit to risk.

14 But certainly the results from the 06
15 trial do not begin to address that issue. You cannot
16 look at the very small subgroup of people who continue
17 to be monitored and in any way interpret those results
18 to be representative of the broader population.

19 So there are no data here that really in
20 any reliable way assess effects beyond 12 weeks, and
21 so essentially what we're left with is a suggestion of
22 modest effects and not proven on the primary endpoint

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 with significant injection site pain and with the hope
2 that possibly there could be longer term effects, but
3 without data to address that.

4 DR. BARST: Can I address several points
5 that were raised by Dr. Fleming's comments?

6 CHAIRMAN BORER: You'll have to use the
7 microphone that works.

8 DR. BARST: I just wanted to address three
9 points that were raised by Dr. Fleming's comments.
10 One, a patient going on Flolan who stopped
11 treprostiniol because of an adverse event does not
12 necessarily mean that the patient was deteriorating or
13 worsened. At the time of the study, it's the only
14 alternative therapy for these patients.

15 When we have a patient who has a life
16 threatening disease and we are stopping an
17 investigational drug and the only alternative is
18 intravenous epoprostenol, it's very difficult to take
19 care of a patient and say, "We're not going to treat
20 you when we have a treatment."

21 Number two, there certainly was a
22 difference in hospitalizations, which is a sign of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 morbidity between the two patients with regard to
2 worsening, right heart failure, and pulmonary
3 hypertension, and I would like, if possible, Dr. Koch
4 to address why we felt it was more appropriate to look
5 at the median difference, which was 16 meters, as
6 opposed to the mean difference of ten meters.

7 CHAIRMAN BORER: If we can keep this
8 analysis brief, that would be good because we're going
9 to have to get on to the questions here.

10 DR. FLEMING: Can we, just in the interest
11 of time, if we grant 16, 16/10 is a critical issue,
12 and I know the committee's discussion time is of
13 essence.

14 Gary, is this something that goes beyond
15 trying to convince us it's 16 rather than ten?

16 DR. KOCH: No. I think all I was going to
17 say is the median is more interpretable because it's
18 more robust to the imputation.

19 DR. FLEMING: I think you can say 16; I
20 think you can say ten. I think it's substantively the
21 same issue. I still would say I'm going to use what
22 it is that was listed as the primary.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 And, by the way, just quickly to respond,
2 your comment is well taken, and that is going on
3 Flolan doesn't necessarily mean it's a bad thing. You
4 were the one who actually put forward the analysis on
5 page 39 though to say that patients who were
6 discontinuing for AEs had a better rate of not going
7 on Flolan than those who were discontinuing to
8 worsening disease.

9 So I was simply following the lead that
10 you had given using that as a measure.

11 CHAIRMAN BORER: Okay. Let's move on to
12 the questions here. We'll go through them, and maybe,
13 Tom, you can lead us and then we'll ask for additional
14 comments.

15 Let me remind everybody because so many
16 editions of these questions have been published
17 somewhere that we want to look only at the set of
18 questions that was attached to the agenda, which on
19 the lower right-hand corner of the page says,
20 "Includes changes through 8 August 2001 at 7:38." I
21 think that's a.m., 0738, a.m.

22 Without going through the preamble here,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the committee is asked if the available data
2 demonstrate clinical benefit and whether the drug
3 merits a role in the treatment of patients with
4 pulmonary hypertension.

5 Number one, the two principal
6 effectiveness studies assessed six minute walking
7 distance and demonstrated effects favoring
8 treprostinil with p values of .061 and .055
9 individually, and .006 pooled, according to the
10 sponsor's analysis.

11 The prospective analysis plan, as we
12 heard, defined other standards.

13 So 1.1: how, if at all, did the following
14 factors make it difficult to show a drug effect?

15 Tom, do you want to go ahead?

16 DR. FLEMING: Well, let me try to do this
17 on the fly since I'm just now looking at the revised
18 version for the first time, although it looks like
19 there's a strong relationship between the two.

20 This is which factors make it difficult to
21 show a drug effect. It's difficult to answer this.
22 Let me just give some general sense responses.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 I think the most important, plausible
2 answer is small effect size. We don't know what the
3 true effect size is. We only have an estimate of
4 that, but it's certainly giving us an important
5 insight into what the true effect size is.

6 So if we interpret the estimated effect
7 size to be the true effect size, whether you consider
8 it ten or whether you consider it 16, it's anywhere
9 from 30 percent to 15 percent what was the targeted
10 effect size in this setting, and I think that's
11 certainly one of the major issues.

12 I think the high withdrawal rate and the
13 asymmetric withdrawal rates are concerns. I don't
14 think these explain a smaller drug effect. They might
15 actually be explaining somewhat of an exaggeration in
16 our estimate of the true drug effect.

17 Tolerance to the study drug is important,
18 and it's certainly possible that if there is a
19 substantial level of nonadherence that follows from
20 lack of tolerance, that that could lead to a reduction
21 in the overall achieved benefit, although that's not
22 an under estimate of truth. That represents what

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 truth is.

2 Some of the things that I would say do not
3 strike me as being --

4 CHAIRMAN BORER: Tom, I think that refers
5 to becoming tolerant to its benefit.

6 DR. FLEMING: Okay. So we'll come back to
7 that. I'd like to hear some other committee members'
8 comments about that.

9 Large placebo effect, I don't think that
10 explains it because, in fact, what we see is, in
11 essence, that the large change over the first week is
12 mirrored by the placebo, and the placebo drops back to
13 zero. So it's not a matter of where we had a 50 meter
14 improvement in intervention and a 40 meter improvement
15 in the placebo arm.

16 Wrong population, it's a very good
17 question as to whether, for example, PPH might have
18 shown a different effect. If we see, for example,
19 with Flolan a 45 meter improvement, maybe we should
20 have looked in PPH, but in fact, the subgroup analysis
21 doesn't suggest that that was influential.

22 Wrong primary endpoint, I'd say not unless

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 you were wanting to directly target effects on
2 mortality, hospitalization, clinical deterioration,
3 which would be more clinically relevant. Obviously
4 though I recognize that such endpoints would be
5 implausible to be able to establish conclusively in
6 all likelihood, although the follow-up may have been
7 too brief.

8 And I realize that it's problematic to use
9 a placebo over an extended period of time in this
10 population, but my sense is that six minute walk or
11 other very clinically relevant phenomena that are the
12 representation of what are the major sequelae of
13 pulmonary arterial hypertension would be more
14 meaningful, but it's problematic to anticipate how you
15 would do a placebo control trial over a long enough
16 time to be able to see such effects.

17 CHAIRMAN BORER: Okay. Let's start at
18 the --

19 DR. TEMPLE: Jeff, can I say something?

20 Suppose it were -- you didn't address this
21 one -- suppose it were true as has been alleged that
22 walking distance at least for people with decent

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 walking distance isn't changed much, but the people
2 walk as much as they want and experience less dyspnea.
3 Are you saying that even if some combination of those
4 two things had been the primary endpoint you wouldn't
5 find it credible?

6 I mean, of course, it wasn't the primary
7 endpoint. That's the problem.

8 DR. FLEMING: Right.

9 DR. TEMPLE: But it doesn't seem
10 inherently nonsensical, right?

11 DR. FLEMING: I think there's a wide array
12 of measures that could have been put forward that
13 would have been inherently reasonable, and the focus
14 that I would take always is what is it that we said in
15 advance because it's always easy when there are a wide
16 array of measures that could be used to look at those
17 in retrospect and be particularly persuaded by those
18 that look most impressive.

19 If it's very obvious that there's a
20 combination of measures that really most adequately
21 and effectively represent what is truly most
22 clinically relevant to this patient population and are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 adequately sensitive, interpretable, and measurable,
2 those should have been the primary endpoints.

3 And what I can say is there clearly are
4 other measures beyond the six minute walk that are
5 relevant, and some of those measures show more
6 encouraging effects, although by my sense they're of
7 modest magnitude.

8 There are even more clinically relevant
9 measures, such as mortality and transplantation and
10 serious clinical deterioration, and those didn't show
11 effects. Maybe they would have if we had gone over a
12 much longer period of time, but we didn't.

13 CHAIRMAN BORER: Okay. We'll start at my
14 left, and if you have comments that add to what Tom
15 has said or disagree in any way, let's make those now.

16 I think, Alan, are you at the end there?

17 DR. HIRSCH: No major comments.

18 CHAIRMAN BORER: Paul?

19 DR. ARMSTRONG: Pass.

20 CHAIRMAN BORER: I would suggest only that
21 I think the high inter-subject or intra-subject
22 variability issue is an important one because I agree

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 with what Tom said about the endpoints that were used.
2 It's not clear to me how if one is trying to diminish
3 or show that a drug diminishes symptoms you can do
4 that, and that is a good thing to do, make people feel
5 better; how you can do that easily with measures that
6 inherently have a high variability.

7 And I think that the measures that were
8 chosen do have a high variability inherently among
9 subjects, and that that makes it very difficult to
10 show a drug effect.

11 Maybe we'll come back to that later, but
12 I think that that's another important issue in
13 determining why we may or may not have seen what we
14 hoped to see here. Fifty-five meters was the expected
15 effect. I'm not sure why that was selected. I know
16 nominally why it was selected, but I think perhaps it
17 was a misselection given what was known from available
18 data. It may have been an over optimistic
19 expectation.

20 In any event, other than that, let's go
21 down at the other end there. Who is at the other end?

22 Well, okay. Dr. Brem.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. BREM: The only comment that I would
2 make is if one accepts the sponsor's view that there's
3 a progressive increase in dose that is not tolerance,
4 but in fact is titrating to effect, and that that
5 effect takes more than three months, would it have
6 been better to make one's study of specific endpoints
7 at a later date, in other words, at six months, for
8 instance, if that were possible?

9 I acknowledge what has been said. It's
10 very difficult to do a placebo controlled study over
11 a longer period of time because people are sick, and
12 you're ethically restrained in withholding treatment
13 from them. But, in fact, it would have been very
14 interesting to see if on the titrated effective dose
15 you did see a more pronounced difference in the walk
16 and the other measures of the study.

17 CHAIRMAN BORER: Steve.

18 DR. NISSEN: Well, obviously there's a lot
19 of uncertainty here, but I'd like to focus on a couple
20 of points. With a drug where there is a clearly very
21 demonstrable side effect like pain and where the
22 instructions to investigators were to go low, go slow,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 I think you have to ask the question: is the smaller
2 treatment effect that was observed than was estimated
3 there because the investigators, in an effort to
4 protect the patients against symptoms, were going slow
5 and going low?

6 And you know, I'm prepared to accept the
7 possibility that this is as effective an agent as
8 epoprostenol, but I think that we probably didn't see
9 you get to the doses that would have done that mainly
10 because of the study protocol, and you know, I think
11 I agree with several other people that it's
12 unfortunate, but I think that that hurt the efficacy
13 side of the trial.

14 And you know, you can't go back. All you
15 can do is try to understand what happened and what it
16 means.

17 The other thing I want to focus on is the
18 choice of population. In going for a broader
19 population than has been previously attempted, you
20 might have biased against the study. I mean,
21 congenital heart disease patients are probably more
22 resistant, and so now, you know, all of your sample

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 size estimates are based, I presume, on the assumption
2 that you'd see the same treatment benefit across the
3 entire study, and that might have been a bad
4 assumption, and probably in retrospect I can't prove
5 that, but it probably was a bad assumption.

6 And so I think that the study design may
7 actually have masked effectiveness for a drug that
8 could well be every bit as effective as the
9 intravenous form of this agent, and actually creates
10 obviously a big quandary for me and for others because
11 we have to decide, you know, what to do here.

12 And I think for me understanding why the
13 treatment effect was small is very important, and
14 those two factors come to the fore with me.

15 There's one other comment I wanted to
16 make, and that is that I must say I'm not
17 overwhelmingly impressed by the whole six minute walk
18 test approach. You know, the notion that dyspnea
19 limits exercise may, in fact, not be entirely the
20 case, particularly in a non-encouraged test, and you
21 know, I think there are some lessons to be learned
22 here about how do you test, you know, these kinds of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 drugs in the future. I'm not sure that the test was
2 the best test.

3 CHAIRMAN BORER: Okay. Dr. Anderson?

4 DR. ANDERSON: I only have one concern at
5 this time. I think some of the questions that
6 apparently are being raised appear to be related to
7 the study design, but I'm just coming into this whole
8 process. So I'd rather listen a little bit more.

9 CHAIRMAN BORER: Michael

10 DR. ARTMAN: Most of my questions and
11 concerns have been addressed, but one point that did
12 not come up really was the effect of age on either
13 safety or efficacy or dropouts, and one could imagine
14 that perhaps most of the people who dropped out
15 because of pain at the injection site may have been
16 teenagers or something and just didn't want to put up
17 with it.

18 Do you have data that can help us one way
19 or the other about the role of age on safety and
20 efficacy?

21 We've seen different diseases. You had a
22 pretty wide spectrum of age from eight to 75 years, I

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 believe. Is there any information there that could
2 help us?

3 CHAIRMAN BORER: While you're looking,
4 Alan?

5 DR. HIRSCH: Well, you know, I just was
6 responding a little bit to the comments I've already
7 heard. So instead of passing I'm going to come back.
8 I think for the record, you know, we do provide a
9 public service in giving our opinions as to what's
10 approvable and how we approach the disease. So I'm
11 going to respond to the earlier comments.

12 And this is meant also for the Pulmonary
13 Hypertension Association members who have been kind
14 enough to come here and who will carry this dream
15 forward of better treatments.

16 I hope that when we come here and for
17 myself personally that we're very generous with
18 methods of measuring clinically significant outcomes
19 in this really horrific disease, and to be specific
20 and to echo some of the things Steve said, I am not
21 worried, Steve and Tom, about the choice of
22 measurement outcomes, whether there's a six minute

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 walk, a Borg score. There's many ways of measuring
2 symptomatic benefit.

3 For those who know me, one can show
4 benefit and the patients feel better; I'm happy. So
5 the choice of endpoints may be a bit unfortunate, but
6 they're acceptable to me.

7 Combinations of endpoints, ways of mixing,
8 Gary, symptoms and walking times is okay with me, and
9 additionally, relatively small benefit changes over
10 time are all right with me because it's hard to place
11 value on that change. I'd rather have the patients
12 and physician in the office make that determination,
13 not me on the pane.

14 And then finally back to the comment. I
15 don't mind if it takes three months or six months to
16 improve. When one looks at a dismal outcome, it's
17 okay to have hope and to take time to get to a
18 positive endpoint. That's generous, I hope.

19 But at the end of that we have to
20 unambiguously achieve the endpoint. So like we've all
21 said along the panel, when you have a predefined plan,
22 as you said, Tom, and you set those rules that are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701