DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL

DRUGS ADVISORY COMMITTEE

+ + + + +

93rd MEETING

+ + + + +

THURSDAY,

AUGUST 9, 2001

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The Advisory Committee met in the Jack Masur Auditorium, Building 10, Clinical Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, at 8:30 a.m., Jeffrey Borer, M.D., Chairman, presiding.

PRESENT:

JEFFREY BORER, M.D., Chairman

MICHAEL F. ARTMAN, M.D., Member

THOMAS FLEMING, Ph.D., Member

ALAN HIRSCH, M.D., Member

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ORIGINAL

JoANN LINDENFELD, M.D., Member

PAUL ARMSTRONG, M.D., Member

STEVEN NISSEN, M.D., Member

PRESENT (Continued):

JEFFERY KOPP, M.D., Guest

GLORIA ANDERSON, Guest

ANDREW BREM, M.D., Guest

JOAN C. STANDAERT, Executive Secretary

FDA MEMBERS PRESENT:

ROBERT TEMPLE, Director, Office of New Drug Evaluation

Raymond Lipicky, Director, Cardiovascular and Renal Drugs Division

ALSO PRESENT:

STUART RICH, M.D.

ROBYN BARST, M.D.

SALIM MUJAIS, M.D.

MARSHA WOLFSON, M.D.

FRANK OGRINC, Ph.D.

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

2 (8:37 a.m.)

3 CHAIRMAN BORER: With even greater
4 trepidation, I welcome everyone to the 93rd meeting of
5 Cardiovascular and Renal Drugs Advisory Committee of
6 the Division of Cardiorenal Drug Products of the U.S.
7 FDA.

8 The meeting is now open for public
9 comment. Oh, sorry. The issue of conflict of
10 interest will be reviewed by Joan Standaert, the
11 Executive Secretary of the committee.

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

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

1 following exceptions.

2 In accordance with 18 USC 208(b)(3), full
3 waivers have been granted to Drs. Alan Hirsch, Thomas
4 Fleming, Jeffrey Borer, and JoAnn Lindenfeld, which
5 permits them to participate in all official matters
6 concerning Remodulin. A copy of the waiver statements
7 may be obtained by submitting a written request to the
8 agency's Freedom of Information Office, Room 12A-30 of
9 the Parklawn Building.

10 In addition, Dr. Hirsch's institution, the
11 University of Minnesota Medical School is involved in
12 unrelated studies sponsored by United Therapeutics and
13 Glaxo SmithKline. Although these interests do not
14 constitute financial interest in the particular matter
15 within the meaning of 18 USC 208, they could create
16 the appearance of a conflict.

17 However, it has been determined,
18 notwithstanding these interests, that it is in the
19 agency's best interest to have Dr. Hirsch to
20 participate in the committee's discussions concerning
21 Remodulin.

22 In the event that the discussions involve

1 any other products or firms not already on the agenda
2 for which an FDA participant has a financial interest,
3 the participants are aware of the need to exclude
4 themselves from such involvement, and their exclusion
5 will be noted for the record.
6 With respect to all other participants, we
7 ask in the interest of fairness that they address any
8 current or previous financial involvement with any
9 firm whose products they may wish to comment upon.
10 That concludes the conflict of interest
11 statement for August 9th, 2001.
12 CHAIRMAN BORER: The meeting is now open
13 for public comment. Is there anyone who would like to
14 say anything?
15 We've had some applications from several
16 people. First, is Linda Carr here? Yes, okay.
17 Ms. Carr, before you speak, I'm going to
18 ask you and anyone else who speaks to disclose any
19 relevant financial interests and to make public
20 whether the trip here was subsidized in any way by
21 some commercial interest.
22 MS. CARR: I'm sorry. I just walked in.

1 Members of the committee, thank you for
2 the opportunity to speak before you today and
3 participate in the review process for the approval of
4 the new drug for the treatment of pulmonary
5 hypertension.
6 I'm Linda Carry. My 14 year old daughter
7 has primary pulmonary hypertension, and she's been
8 treated with Flolan for seven years.
9 I am also president of the Pulmonary
10 Hypertension Association. At this time, PHA has a
11 membership of over 3,700 patients, care givers, and
12 medical professionals. More than 70 support groups
13 have been organized around the country and
14 internationally.
15 A little over ten years ago, when three
16 isolated PH patients came together and founded PHA,
17 there were very few diagnosed cases of PH. We are
18 told the number was less than 200.
19 Today PHA supports an active and growing
20 patient run 800 line and a scientific advisory board
21 made up of 21 pulmonologists, cardiologists, and other
22 experts in treating PH.

1 PHA is currently working with NIH in a
2 growing collaborative research grant effort through
3 the KO-8 program, which hopefully will bring us closer
4 to a cure for PH.
5 PH also funds a research fellows awards
6 program geared towards encouraging young researchers
7 at the front end of their careers to become involved
8 in and committed to finding better treatments and a
9 cure, but we are not there yet.
10 After careful consideration on the part of
11 the PHA board, which is comprised of patients,
12 caregivers, and physicians treating the disease, it
13 was decided that it was important for PHA to be here
14 today so that patients and family members who live and
15 die with this terrible illness be represented.
16 Whatever you decide today, these hearings
17 will have a large impact on our lives and the history
18 of this illness. The PHA wants you to know and to
19 state clearly that we support the FDA's role in
20 evaluating new pharmaceuticals, and we depend upon the
21 FDA for the introduction of safe and effective
22 products. We count on the FDA to evaluate the science

1 and make the right decision.

2 Pulmonary hypertension is a life
3 destroying illness. In each of our newsletters, we
4 run pages of memorial listings and passages, our death
5 list. Ours is a rare illness, but death is very
6 common.

7 Doctors have very limited options for
8 treating this disease. At the present time, as you
9 likely know, there's only one FDA approved treatment
10 for PH, and that's Flolan. It's a drug that's
11 administered through an intravenous in-dwelling
12 catheter. My daughter is on that treatment. It's
13 very complex and difficult.

14 It is the Pulmonary Hypertension
15 Association's position that if the science is good,
16 demonstrating that the medications are safe and
17 effective, doctors and their patients do need more
18 options for treating pulmonary hypertension.

19 Once again, I would like to thank the
20 committee for the opportunity to present the view of
21 the Pulmonary Hypertension Association.

22 Thank you.

1 CHAIRMAN BORER: Are there any other
2 public comments?
3 We have applications from two other
4 people, JoAnne Schmidt.
5 MS. SCHMIDT: Good morning, and thank you
6 for the opportunity to address this committee.
7 My name is JoAnne Schmidt and I am 36
8 years old. I was diagnosed with primary pulmonary
9 hypertension in July of 1998.
10 My family history with PPH goes back to
11 1963, when my mother's sister, Josephine, died at the
12 age of 23 and in her first trimester of pregnancy.
13 The term "pulmonary hypertension" was
14 forgotten in our family until 1995, when my older
15 brother John began experiencing classic symptoms of
16 PH, syncope, shortness of breath, and fatigue.
17 After months of tests and visits to all
18 different kinds of doctors, he was diagnosed with
19 pulmonary hypertension. This jogged the family's
20 collective memory, and we requested my aunt's medical
21 record, which confirmed the diagnosis and revealed an
22 awful genetic pattern at work.

1 My brother was placed on Flolan
2 immediately, and within a few months his severely
3 enlarged heart began to recover, and his condition
4 stabilized, and I got to watch my brother go through
5 every step of his treatment.
6 My family and I set out to learn as much
7 as we could about pulmonary hypertension. We joined
8 the Pulmonary Hypertension Association and began
9 making regular donations towards research.
10 1998 comes, and I began to have the same
11 symptoms as my brother, and I was diagnosed in July of
12 that year. In one fell swoop my life changed. I knew
13 immediately that I would never be able to have
14 children, and at 34 years old I had a medical alert
15 bracelet and a handicap parking permit. It was
16 surreal.
17 That August I entered the clinical trials
18 for Remodulin. I made this decision with all of the
19 knowledge of what using Flolan entailed. I had seen
20 the fear on my brother's face when we suspected he'd
21 gotten a line infection. The fear of infection and
22 the large, bulky pump were the main reasons for me

1 wanting to give Remodulin a try.

2 When the trial began, I knew immediately

3 that I had received the drug, not the placebo, as I

4 began experiencing all of the side effects within days

5 of beginning the medication. The pain was very

6 intense in the beginning. My stomach began to swell

7 and redden. My condition didn't change much for the

8 first few months. I had been diagnosed very early

9 compared to most PH patients. So my symptoms weren't

10 that severe yet.

11 I slowly increased my dosage every week.

12 Then in March of 1999, I had a setback and fainted

13 after going outside while it was snowing and having a

14 snowball fight with my husband. My doctor said that

15 my disease had taken a big step forward. It had

16 progressed, and I obviously wasn't getting a

17 therapeutic dosage of Remodulin yet, and she said,

18 "I'll give you some time. I'll give you a few months,

19 but if you don't improve, we should look at Flolan."

20 So I stepped up my increases after that.

21 I was determined not to go on Flolan. Remodulin gave

22 me freedom that I could see that my brother didn't

1 have. I never worried about infection. My pump was
2 carefully tucked away and no one could see it, and I
3 could swim with a watertight case.
4 The fact that I could hide my pump was
5 very important to me. At the time I was diagnosed, I
6 was a vice president with a major New York bank and
7 presented to corporate clients on a regular basis, and
8 having a small pump, I was able to conceal any
9 evidence of my condition and proceed with business as
10 usual.
11 In July of 1999, I was retested. My heart
12 function had improved significantly, and my cardiac
13 output was increased, and my doctor was satisfied that
14 I had reached a therapeutic level of Remodulin.
15 I was ecstatic. I had integrated the pump
16 and Remodulin into my lifestyle, and I was feeling
17 much, much better, and that summer I was able to do
18 lots of gardening and swimming and also sorts of other
19 activities.
20 In March of 1999, together with my family,
21 we formed the Long Island, New York Support Group for
22 Pulmonary Hypertension, and we now have over 50

1 patients in our group. I've developed a pretty good
2 knowledge of what each treatment entails, and I can
3 tell you hands down that Remodulin is the simpler,
4 less invasive delivery method for pulmonary
5 hypertension.
6 It takes me five minutes to fill a syringe
7 with Remodulin and change my site, and I sit next to
8 my sister-in-law while she prepares -- she's a nurse,
9 and she prepares my brother's medicine every night,
10 and she carefully mixes and fills the cassette, and it
11 takes so much longer than my regime.
12 The patients on Flolan have more flushing,
13 diarrhea, jaw pain and foot pain than I do, and I
14 realize that each patient has a different experience,
15 but I can tell you that my brother and everyone else
16 on Flolan in our support group looks enviously at me
17 and my pump, and they long for the day that they can
18 be switched over to Remodulin.
19 Having grown up on Long Island, my brother
20 and I are water babies. We were taught to swim at
21 five years old in the Great South Bay. The ocean and
22 swimming is in our blood, and it breaks my heart that

1 my brother and I can't do this together anymore.

2 In October, my husband Ken and I will

3 accompany my brother and his family to Cancun for the

4 third year in a row, and for the third year in a row,

5 my brother will have to watch me play with his

6 daughters in the pool and in the ocean.

7 Remodulin has allowed me to have almost a

8 normal life, and I hope you approve Remodulin so that

9 all of the newly diagnosed PH patients get the same

10 chance that I did, and that is a choice for the

11 treatment that works best for them.

12 I'd be happy to answer any questions that

13 you have for me.

14 CHAIRMAN BORER: Any questions or comments

15 from the committee?

16 No? Thank you very much. Oh, go ahead.

17 DR. BREM: Do you still have any abdominal

18 pain when you have the infusion?

19 MS. SCHMIDT: I'll occasionally hit what

20 I'll call a bad site, but the pain was intense in the

21 beginning and completely manageable now.

22 DR. BREM: Manageable in what way? What

1 do you take for it?

2 MS. SCHMIDT: If I hit a bad site, I take

3 Tylenol. I take Tylenol, and if it happens to be

4 incredibly sore, I might use an ice pack for a little

5 while.

6 DR. BREM: Is that every day or --

7 MS. SCHMIDT: No.

8 DR. BREM: How would you characterize it?

9 MS. SCHMIDT: How would I characterize how

10 often I get a bad site?

11 DR. BREM: Yeah, and how often is the pain

12 -- does it require medication, for instance? On a

13 weekly basis, would you say two days a week?

14 MS. SCHMIDT: No, I would say more like

15 twice a month maybe.

16 DR. TEMPLE: When you didn't get a

17 response initially and gradually raised your dose,

18 what did you get up to? Do you remember what dose you

19 got to?

20 MS. SCHMIDT: My highest dosage?

21 DR. TEMPLE: Yes.

22 MS. SCHMIDT: My highest dosage was 88

1 nanograms, and now I'm down to 80.

2 DR. TEMPLE: So once you found a dose that

3 seemed to be okay, you didn't find you had to keep

4 increasing it?

5 MS. SCHMIDT: Yeah. What happened was I

6 went to 88 nanograms, and I have a very swollen tummy.

7 My tummy is swollen, and I talked my doctor into

8 saying can we scale back a little bit and see what

9 happens. So that's kind of settled down at 80

10 nanograms.

11 CHAIRMAN BORER: Okay. Thank you very

12 much.

13 MS. SCHMIDT: Thank you.

14 MS. DeSERANO: Hello.

15 CHAIRMAN BORER: Beth DeSerano?

16 MS. DeSERANO: Correct. Good morning,

17 members of the committee. I'd like to thank you for

18 allowing time for my statement.

19 My name is Beth DeSerano. I'm 36 years

20 old also, coincidentally like JoAnne, who I just met

21 yesterday.

22 I traveled from Marion, Iowa to briefly

1 share my experience and thoughts on a life changing
2 medication known to me as UT-15, now to be known as
3 Remodulin.
4 In October of 1997, my life changed
5 forever. After an unexpected trip to the local
6 emergency room. X-rays showed an enlarged heart, and
7 further testing led to the diagnosis of a rare disease
8 I had never heard of called primary pulmonary
9 hypertension.
10 I was put on oxygen, sent home by the
11 local doctors, and told to, quote, get my affairs in
12 order, unquote. These doctors and cardiologists
13 predicted I had six months to live. Devastation and
14 fear.
15 Not willing to accept such a fatalistic
16 diagnosis, I sought out a second opinion. Through the
17 Internet, I found the name Dr. Stuart Rich, kept
18 coming up in journal articles and through the PH
19 Association. He was a leading PH specialist within
20 four hours' drive of my home.
21 The test he authorized confirmed my
22 initial diagnosis, as well as showed I was a

1 nonresponder to CCBs, which are calcium channel
2 blockers, a much simpler form of treatment for early
3 primary pulmonary hypertension.
4 Dr. Rich told me about Flolan, the only
5 medication currently approved at that time, and it was
6 showing positive effects in many of his patients, but
7 he also happened to mention a chance to enroll in a
8 clinical trial for an experimental medication, UT-15,
9 also known as Remodulin.
10 After taking a short while to weigh my
11 options, it seemed that UT-15 was the obvious choice
12 for me. I felt that the small pump and the easy
13 subcutaneous delivery method was superior to the bulky
14 Flolan pump and the continuous risk of line infections
15 that I have heard from all patients at the Hickman
16 site.
17 I enrolled in the trial, and although I
18 did exhibit side effects in the early months of use,
19 I can now say that the positive changes in my
20 breathing and stamina have far outweighed the side
21 effects that I used to experience.
22 Today I exhibit no consistent side effects

1 from the medication Remodulin. Even pain at the
2 subcutaneous delivery sites is completely nonexistent
3 for me.
4 As a note, I am on no medication. I take
5 Tylenol for headaches, which I don't -- am not sure
6 are a side effect of the condition, medication, or
7 just general stress in my life. I'm not sure.
8 Before Remodulin, I couldn't walk up a
9 single flight of six stairs leading from my front door
10 to the upper level of my split level home without
11 gasping for air. Right now I'm gasping because I'm
12 nervous.
13 Even walking from my bedroom to the
14 bathroom was daunting at times. Now I climb stairs,
15 take walks to the park with my daughter and pull her
16 in her wagon.
17 Before Remodulin, fainting and dizziness
18 resulted from even minor exertion. Chest pain and
19 palpitations were constants in my life. I took them
20 to be normal.
21 Now fainting and extreme dizziness are
22 just memories. Remodulin, combined with a positive

1 mental focus and faith in God, and faith also in
2 focusing on stress reduction, lets me walk talk and
3 proud and breathe very easily.
4 Before Remodulin, lying flat on my back in
5 bed was like suffocating. Sleep was minimal unless I
6 was almost sitting completely upright. Now, sleep is
7 something that I don't dread. I'm comfortable in any
8 position.
9 Flolan offers one alternative, but I
10 believe that PH patients deserve another.
11 I have felt what dying is like. I truly
12 can say that, but I can also say with complete
13 assurance that Remodulin has allowed a rebirth for me.
14 I may suffer from a fatal disease, but
15 Remodulin give me the ability to live life again. I
16 believe I will live to see my daughter graduate from
17 high school and marry in years to come, a hope that I
18 never had before this drug.
19 Please vote to approve Remodulin so that
20 other PH patients can have what I have: hope and a
21 future.
22 Thank you.

1 I will also accept any questions the
2 committee may have.
3 CHAIRMAN BORER: Any issues that anyone
4 wants to raise? Questions? No?
5 Thank you.
6 MS. DeSERANO: Thank you.
7 CHAIRMAN BORER: Before we go on, because
8 the subsequent comments will be read by Joan
9 Standaert, they were sent in written. I'm assuming
10 that we heard nothing about conflict of interest or
11 funding of the trip because there is no conflict of
12 interest or funding by the companies involved here.
13 PARTICIPANTS: Right.
14 CHAIRMAN BORER: That's correct.
15 Okay. There were two comments that were
16 sent to the committee that will be read by Joan
17 Standaert.
18 MS. STANDAERT: Now, this is a comment
19 from, I believe, Laboni Mahfuz. You'll have to excuse
20 my pronunciation.
21 "I, Laboni Mahfuz, have been on UT-15 sine
22 August 1999. I have secondary pulmonary hypertension.

1 This medicine is keeping me active and letting me
2 delay the lung transplantation.
3 "I used to get short of breath climbing
4 stairs. Now I can climb stairs without any problem.
5 I have more energy to do most of the household things
6 that I don't like to do and my hobby, gardening and
7 painting. I am also taking one or two courses at the
8 college.
9 "I believe this medicine will help many
10 patients like me breathe better and enjoy a better
11 quality of life."
12 This gentleman resides in Garland, Texas.
13 There is another statement from Shelly
14 Shapiro. He is one of the physicians participating in
15 the UT-15 drug studies. He states that he has 15
16 patients chronically on the drug for treatment of
17 primary and secondary pulmonary hypertension.
18 "I also have 40 patients on chronic Flolan
19 for PH as well. I am clearly not an entirely unbiased
20 observer because of my role in the study. However, I
21 have had an opportunity compare managing patients on
22 Flolan and UT-15.

1 "There are clear benefits from the
2 subcutaneous administration, which I feel outweigh the
3 problem with the site pain. It is considerably easier
4 for patients to start and learn UT-15. The catheter
5 related problems, infections, mixing problems, are all
6 significantly less with UT-15.
7 "There are a significant number of
8 patients who we can't start on" -- I guess it means
9 "of Flolan because the support systems can't be gotten
10 in place or the patients need to start on Flolan
11 acutely. But patients who are less impaired benefit
12 from out-patient initiation of UT-15.
13 "Although all of our patients are given
14 prescriptions for Vicodan or Tylenol plus codeine, the
15 actual use of these drugs is limited to the days with
16 the worst site pain, usually one through five, and
17 most scarcely use narcotics after being on drug for
18 four months.
19 "I think both Flolan and UT-15 are
20 critical drugs in the management of PH. UT has been
21 very effective for most of the patients we have on it,
22 and the concerns about the site pain are more than

1 compensated for by the life style issues.

2 "I hope that you will share this with the

3 committee evaluating UT-15."

4 CHAIRMAN BORER: Thank you.

5 Are there any other comments?

6 (No response.)

7 CHAIRMAN BORER: We have a request for

8 public comment regarding Extraneal, but with the

9 permission of the commenter, I'd like to hold that

10 until after lunch when we actually discuss Extraneal

11 so that the comment will be relevant to the ensuing

12 discussion.

13 If there are no other comments, we'll

14 begin the presentations from United Therapeutics, to

15 be introduced by Roger Jeffs, Dr. Roger Jeffs from

16 United Therapeutics.

17 DR. JEFFS: Good morning, Mr. Chairman,

18 Dr. Temple, Dr. Lipicky, and distinguished members of

19 the panel. We are pleased today that you will be

20 considering the NDA for treprostinil sodium or

21 Remodulin injection developed as a subcutaneous

22 treatment for patients with pulmonary arterial

1 hypertension.

2 The development program for treprostinil
3 represents the largest placebo controlled program ever
4 conducted in patients with pulmonary arterial
5 hypertension.

6 Our presentation today will review the
7 efficacy and safety data from our chronic dosing
8 trials. Dr. Stuart Rich, professor of medicine and
9 Director of the Rush Heart Institute, Center for
10 Pulmonary Heart Disease at Rush Presbyterian, St.
11 Luke's Hospital in Chicago, will present the efficacy
12 data from our controlled trial experience, which
13 includes data from 496 patients.

14 Dr. Robyn Barst, professor of pediatric
15 cardiology and Director of Pulmonary Hypertension
16 Center at Columbia Presbyterian Medical Center, will
17 present the safety data from our long term controlled
18 and open label studies, which includes data from 679
19 patients who were exposed to treprostinil.

20 Dr. Rich and Barst are heads of two of the
21 largest pulmonary hypertension centers in the country
22 and have been instrumental in the design, conduct and

1 analysis of all clinical studies with treprostinil.
2 United Therapeutics is also joined today
3 by Dr. Gary Koch of the University of North Carolina,
4 Department of Biostatistics, who assisted in the
5 statistical design and analysis of the pivotal
6 studies.
7 Also, Drs. Tom Wenger, Alan Lye
8 (phonetic), and Shelly Chang (phonetic), each of whom
9 participated in the compilation of data for the
10 treprostinil NDA, are available to assist with
11 responding to questions from the committee in their
12 respective areas of expertise.
13 At this time I'm very pleased to welcome
14 Dr. Stuart Rich as our first presenter this morning.
15 CHAIRMAN BORER: While you're coming up,
16 Dr. Rich, because our time is limited with a second
17 presentation this afternoon, I'm going to ask that
18 committee members, unless we have some really burning
19 issues to raise, let's take notes and ask the
20 questions when the speaker is done so that we can
21 minimize the time that we take during the
22 presentations before our own discussion.

1 Having said that, Dr. Rich.

2 DR. RICH: Thank you.

3 I am pleased to present to you a summary
4 of the evidence supporting the efficacy of
5 treprostinil for the treatment of pulmonary atrial
6 hypertension. According to a recent reclassification
7 of this disease at a World Health Organization
8 sponsored symposium in 1998, the term "pulmonary
9 arterial hypertension now includes primary pulmonary
10 hypertension, as well as pulmonary hypertension
11 associated with collagen vascular disease, congenital
12 systemic to pulmonary shunts, drugs and toxins such as
13 diet pills, portal hypertension, and HIV infection.

14 In the past, patients with these
15 associated disorders were considered to have a form of
16 secondary pulmonary hypertension. The clinical
17 manifestations of pulmonary arterial hypertension and
18 its treatments are similar regardless of the etiology.
19 Differences in clinical features of these patients
20 generally related to the specific associated
21 conditions.

22 This slide summarizes the clinical

1 symptoms of pulmonary hypertension as described in the
2 National Institutes of Health registry on PPH.
3 Initial refers to the symptoms that the
4 patients showed at the onset of their disease.
5 Eventual refers to the symptoms that they report at
6 the time they presented to the referring center.
7 The treatments that are commonly used in
8 the management of patients with pulmonary arterial
9 hypertension include digitalis, diuretics,
10 vasodilators, anticoagulants, and epoprostenol. With
11 the exception of epoprostenol, none of the treatments
12 have been evaluated by prospective, randomized
13 clinical trials.
14 Epoprostenol is currently the only FDA
15 approved treatment of patients with pulmonary arterial
16 hypertension. It is administered via continuous
17 intravenous infusion, and is indicated for the
18 treatment of New York Heart Association Class III and
19 IV patients with primary pulmonary hypertension and
20 pulmonary hypertension associated with the scleroderma
21 spectrum of the disease.
22 The efficacy of epoprostenol was

1 established in two randomized, open label clinical
2 trials, one in patients with PPH and one in patients
3 with scleroderma. Both trials show that the
4 intravenous epoprostenol improved symptoms of
5 pulmonary hypertension, exercise tolerance as measured
6 by a six minute walk test, and hemodynamics.
7 However, intravenous epoprostenol therapy
8 is associated with significant clinical risks. The
9 most common are those related to placement and
10 maintenance of an in-dwelling Hickman catheter, but
11 these include pneumothorax, sepsis, and embolization.
12 In addition, the infusion of epoprostenol
13 carries with it the risk of cardiovascular collapse if
14 there is any inadvertent interruption of the
15 intravenous therapy due to problems with the infusion
16 pump system. This risk is related to the very short
17 half-life of epoprostenol.
18 These risks which prevent many patients
19 from receiving epoprostenol led to the development of
20 treprostinil. The brand name is Remodulin, and other
21 designations have been UT-15, Uniprost, and
22 treprostinil.

1 As a prostecycline analogue, treprostinil
2 shares the vasodilator and flavin inhibiting
3 properties of epoprostenol, as well as its
4 hemodynamics effects in patients with pulmonary
5 hypertension.
6 However, unlike epoprostenol, it is
7 clinically stable at neutral pH and room temperature
8 and has a half-life when administered subcutaneously
9 of approximately three hours. These characteristics
10 allow for a less complex and less risky delivery
11 system.
12 These are two of my patients with PPH on
13 epoprostenol therapy. The slide shows the supplies
14 necessary to reconstitute and administer the
15 epoprostenol on a daily basis. The medication must be
16 handled under sterile conditions, and it takes about
17 30 minutes to reconstitute and prepare the cassettes
18 each day.
19 It is delivered by a Hickman catheter and
20 a CAD infusion pump, which is about the size of a
21 portable CD player. The pump and cassette are kept
22 cool by using cold packs which are changed throughout

1 the day.

2 In contrast, treprostinil is premixed into

3 a small syringe and changed once daily into this mini

4 Medpump, about the size of a pager or cell phone.

5 Only aseptic technique is necessary at the injection

6 site, which is usually changed every three days.

7 The needle is similar to a small, 25

8 gauge, four millimeter tuberculin needle.

9 The differences between the two delivery

10 systems are summarized on this slide. Treprostinil is

11 given subcutaneously rather than intravenously. The

12 catheter is implanted by the patient rather than by a

13 surgeon, and it's changed by the patient every three

14 days.

15 There is no risk of thrombus formation, no

16 need for sterile mixing conditions, and a low

17 likelihood of cardiovascular collapse if the infusion

18 is interrupted due to the relatively long half-life of

19 the drug. Sepsis has to date not been reported from

20 the catheter, and the pump is quite small.

21 There have been three placebo controlled

22 efficacy studies with treprostinil in patients with

1 pulmonary arterial hypertension. The first placebo
2 controlled study was a pilot trial, Study 03, which
3 involved 26 patients with primary pulmonary
4 hypertension who were treated for eight weeks. This
5 was followed by the two pivotal trials, Study 04 and
6 05, which together enrolled 470 patients with
7 pulmonary arterial hypertension, who were treated for
8 12 weeks.
9 Patients completing these placebo
10 controlled studies were allowed to continue therapy in
11 an open label extension study, Study 06, which
12 enrolled 631 patients. Of these, 208 patients were
13 entered directly into the open label study without any
14 prior participation in a placebo controlled trial.
15 This slide summarizes the effects of
16 treprostinil in the pilot Study 03, which enrolled
17 patients with the pulmonary hypertension with Class
18 III and IV symptoms.
19 Treprostinil produced favorable effects on
20 a variety of efficacy measures although none of these
21 differences reached statistical significance since
22 only 26 patients were enrolled.

1 Based on these encouraging results, two
2 identical international, multi-center, double blind,
3 randomized, parallel group, placebo controlled
4 studies, Studies 04 and 05, were carried out to
5 evaluate the efficacy of subcutaneous treprostinil
6 plus conventional therapy as compared with
7 conventional therapy alone in patients with pulmonary
8 arterial hypertension. These trials were carried out
9 in 40 medical centers across 13 countries. It is the
10 largest clinical trial ever conducted in patients with
11 pulmonary hypertension, and the first large scale
12 study that was double blind and placebo controlled.
13 This slide summarizes the entry criteria
14 of these two trials. In contrast with other trials
15 with epoprostenol, these two trials with treprostinil
16 enrolled a broad range of patients with pulmonary
17 arterial hypertension. These included not only
18 patients with primary pulmonary hypertension, but also
19 patients with collagen vascular disease and congenital
20 heart disease.
21 Furthermore, the trial did not focus only
22 on patients with Class III and IV symptoms, but also

1 included patients with Class II symptoms. All of the
2 patients had the diagnosis of pulmonary hypertension
3 confirmed hemodynamically. Many of these patients
4 were candidates for epoprostenol therapy, but elected
5 to enroll in these controlled studies.
6 This slide displays the design of the two
7 trials. Patients were required to be stable on
8 standard therapy for pulmonary arterial hypertension
9 for one month prior to randomization, and standard
10 therapy was maintained during the 12-week trial unless
11 otherwise clinically indicated.
12 Patients in meeting the entry criteria
13 were randomized one to one to placebo plus standard
14 therapy or to treprostinil plus standard therapy.
15 Therapy was instituted in the hospital to allow
16 monitoring of vital signs and tolerability.
17 Patients were discharged at the discretion
18 of the investigator and underwent a variety of
19 predefined clinical assessments as shown at the bottom
20 of the slide at weeks one, six, and 12. Four hundred
21 and 70 patients were randomized into the two studies.
22 The efficacy measures used in these trials

1 included exercise capacity as determined by a six
2 minute walk test, signs and symptoms of pulmonary
3 hypertension, a dyspnea-fatigue rating, the frequency
4 of clinical deterioration, the Borg dyspnea score,
5 hemodynamics measured at cardiac catheterization, and
6 a quality of life survey.
7 These have become standard measures of
8 efficacy in clinical trials in patients with pulmonary
9 hypertension.
10 First, I'd like to describe the six minute
11 walk test. We took great care in performing this test
12 to minimize bias and the possibility of unblinding.
13 The test was an unencouraged test, which was always
14 conducted by an independent assessor before any other
15 study assessments at each visit. The assessor was not
16 involved with the care of the patient or with any
17 other study assessment and did not discuss their
18 disease or treatment with the patient.
19 The results of the six minute walk test
20 were never made available to either the investigator,
21 the patient or the sponsor during the conduct of the
22 trial as they were recorded on separate reporting

1 forms and kept in separate locked files.

2 Immediately following the completion of
3 the walk test, the assessor asked the patient to grade
4 the severity of the worst symptom the patient had
5 during the test using the Borg dyspnea scale. The
6 single score was selected from a ten point scale where
7 a higher score reflected a greater severity of
8 symptoms.

9 In this manner the assessor was able to
10 evaluate exercise tolerance both in terms of distance
11 and symptoms.

12 The study also evaluated eight symptoms
13 and eight signs of pulmonary arterial hypertension.
14 These were noted by the investigator as being present
15 or absent at specific visits. Thus, a change
16 represented either the development of a new symptom or
17 sign or the complete resolution of a preexisting
18 symptom or sign.

19 This slide lists the symptoms and signs
20 that were evaluated in the study. They were derived
21 from the experience of the NIH registry on primary
22 pulmonary hypertension as being characteristic of

1 pulmonary arterial hypertension.

2 The dyspnea-fatigue rating was a physician
3 based assessment that was used to evaluate the
4 magnitude of dyspnea and fatigue and the resulting
5 clinical impact. It consisted of three components.
6 Each was given a rating from zero to four that was
7 used to calculate a composite score. It included the
8 magnitude of the task at a normal pace, the magnitude
9 of the pace, and functional impairment with general
10 activities. The lower the score, the more symptomatic
11 the patient.

12 The scoring of one of the three
13 components, the magnitude of task component, is shown
14 here, and as you can see, it closely resembles the
15 approach used to quantify a patient's New York Heart
16 Association functional class.

17 All of the patients underwent hemodynamic
18 measurements with cardiac catheterization at baseline
19 and week 12. The catheterization was performed only
20 after all other efficacy parameters were measured to
21 minimize any potential bias.

22 Quality of life was assessed using the

1 Minnesota Living with Heart Failure questionnaire.
2 This assessment was added at the request of the FDA
3 after the study began and, therefore, was not
4 evaluated in all patients. It measured their
5 perspective of the disease on daily living and
6 included physical, emotional, and global dimensions.
7 the patient answered 21 questions according to a zero
8 to five response scale. Here a lower score was
9 better.
10 This slide lists the prespecified
11 endpoints in the two trials. The primary endpoint for
12 both studies was exercise capacity as determined by
13 the six minute walk test.
14 In addition, the protocol identified five
15 secondary endpoints. The FDA expressed a strong
16 interest in three of these endpoints because of their
17 clinical relevance.
18 As a result, they were designated in the
19 protocol as principal reinforcing endpoints and are
20 identified in this slide by an asterisk. These were
21 signs and symptoms of the disease, the dyspnea-fatigue
22 rating, and the frequency of clinical deterioration

1 which was defined as death, transplantation, or
2 clinical worsening necessitating emergent intravenous
3 rescue therapy.
4 Other secondary endpoints included the
5 Borg dyspnea score and hemodynamics determined at
6 catheterization.
7 This slide summarizes the primary analysis
8 plan for the study, which was agreed upon with the FDA
9 prior to breaking the randomization code. The
10 efficacy population consisted of 469 of the 470
11 randomized patients.
12 One placebo patient dropped out prior to
13 receiving study drug and was not included in the
14 efficacy analysis.
15 For the primary endpoint patients who did
16 not have data at 12 weeks were assigned worst rank if
17 they dropped out because of death, transplant, or
18 worsening symptoms of pulmonary hypertension
19 necessitating intravenous rescue therapy.
20 However, they had their last visit carried
21 forward if they discontinued treatment because of an
22 adverse effect. This is the standard approach that

1 has been used to analyze non-completers in clinical
2 trials of pulmonary hypertension and heart failure.
3 The primary approach used in the analysis
4 of exercise capacity was a nonparametric analysis.
5 Since Studies 04 and 05 were identical in
6 design and recruited similar patients, the sponsor
7 proposed that the studies be analyzed both
8 individually and together. According to the
9 statistical plan, a treatment effect would have been
10 considered to have been demonstrated if both trials
11 reached a p value of less than 0.05 or if the combined
12 trials had a p value of less than .01, and one of the
13 two studies had a p value less than .05.
14 Regardless of the approach, it was
15 anticipated that a favorable effect on the primary
16 endpoint would be supported by favor effects on the
17 principal reinforcing and other secondary endpoints.
18 Again, this analogous algorithm was agreed
19 with the FDA before the code was broken.
20 This slide summarizes the baseline
21 characteristics of the patients enrolled in the
22 trials. The mean age was approximately 45 years, and

1 the patients were predominantly Caucasian and female.
2 About 60 percent of the patients had
3 primary pulmonary hypertension, and about
4 approximately 80 percent of the patients had New York
5 Heart Association Class III symptoms. The treatment
6 groups were well matched for all of these
7 characteristics.
8 Other baseline variables are shown in this
9 slide. Again, the treatment groups were similar with
10 respect to all baseline variables.
11 This slide summarizes the baseline
12 hemodynamics in the patients randomized to placebo or
13 treprostinil. They are characteristic of patients
14 with very severe pulmonary arterial hypertension.
15 This slide shows the use of concomitant
16 treatments for pulmonary hypertension in the patients
17 enrolled in the trial, including anti-coagulants,
18 calcium blockers, other vasodilators, digoxin and
19 diuretics. There were no meaningful differences
20 between the two treatment groups with respect to the
21 use of these background medications.
22 This slide shows the dosing strategy for

1 use for these studies. The starting dose was 1.25
2 nanograms per kilogram per minute. Investigators were
3 instructed to increase the dose gradually over time to
4 a point where the patient reported substantial
5 improvement or resolution in symptoms with acceptable
6 side effects.
7 The infusion rate was increased as needed
8 in increments not to exceed 1.25 nanograms per
9 kilogram per minute per week during the first four
10 weeks, and then not to exceed 2.5 nanograms per
11 kilogram per minute until the end of the study.
12 This strategy allowed the investigators to
13 gauge individually patients' sensitivity to the drug
14 by increasing the dose slowly during initiation of
15 therapy, but once assessed, it permitted doses to be
16 increased more aggressively.
17 Of the 470 patients who were randomized
18 into Studies 04 and 05, 233 patients were randomized
19 to treprostinil and 237 to placebo. One patient
20 randomized to placebo dropped out prior to receiving
21 any study medication due to withdrawal of consent.
22 Of the randomized patients, 33 patients in

1 the treprostinil group and 16 patients in the placebo
2 group failed to complete 12 weeks of a double blind
3 treatment. This difference was entirely due to a
4 difference between the two groups in the number of
5 patients who discontinued treatment because of an
6 adverse event, 18 in the treprostinil group and one in
7 the placebo group.
8 This slide shows the effect of
9 treprostinil on the six minute walk test at weeks one,
10 six, and 12 corrected for placebo for Studies 04 and
11 05 combined. The magnitude of the treatment effect
12 increased from five meters at week one to 11 meters at
13 week six and to 16 meters at week 12, the end of the
14 double blind treatment.
15 At week 12, the median change from
16 baseline, and the difference in the walk distance
17 between the two treatments was 13 meters for Study 04,
18 with a p value of .06; 18.5 meters for Study 05, with
19 a p value of .055; and 16 meters for the two studies
20 combined, with a p value of .0064.
21 Hence, the effects of treprostinil was
22 quite reproducible across the two studies both with

1 respect to the magnitude and statistical significance
2 of the treatment.
3 As a point of information, the committee
4 might be wondering what these results might look like
5 if a parametric analysis had been carried out that
6 assigns zero meters rather than at worst rank to the
7 patients who failed to complete the study due to
8 death, transplant, or clinical deterioration.
9 If this had been done, the treatment
10 difference would have been approximately 20 meters.
11 After review of these data by the FDA,
12 there was agreement between the FDA and the sponsor
13 that the results on the primary endpoint supported the
14 finding of a treatment effect of treprostinil since
15 the p values observed were extremely close, although
16 not quite less than those prespecified in the
17 statistical plan.
18 However, the FDA has questioned the
19 robustness of the finding as well as the clinical
20 meaningfulness of the observed treatment effect. In
21 the next few minutes I'll present analyses that
22 address both of these concerns.

1 First, a question of robustness. As I
2 said earlier, patients who discontinue treatment with
3 a study medication because of an adverse event were
4 analyzed differently than those who discontinued
5 treatment because of clinical deterioration. Those
6 who were withdrawn due to an adverse event, such as
7 infusion site pain, had their last bill (phonetic)
8 carried forward, whereas those who were withdrawn
9 because of a clinical deterioration were assigned
10 worst rank.
11 This determination was made entirely
12 according to the judgment of the investigator and was
13 recorded on the case report form.
14 Nevertheless, one of the FDA reviewers
15 asked whether patients might have been misclassified.
16 Could a patient who was initially tolerating the
17 infusion site pain because of symptomatic improvement
18 subsequently have found the pain to be intolerable
19 because its clinical condition began to deteriorate?
20 Such a patient would have been classified
21 as having withdrawn because of an adverse event when,
22 in fact, he was withdrawing because of a worsening of

1 the underlying disease which only became apparent days
2 or weeks later.
3 The most conservative way of accounting
4 for this possibility would be to reclassify all
5 patients who withdrew because of an adverse event as
6 having withdrawn because of clinical deterioration
7 even though this was not the judgment of the
8 investigator.
9 Given the 18 to one imbalance in
10 withdrawals for an adverse event, such a post hoc
11 reclassification process would have adversely impacted
12 on any finding of a treatment effect on the primary
13 endpoint.
14 The question is: is reclassification
15 warranted? Were patients who were being reportedly
16 withdrawn for an adverse effect actually clinically
17 deteriorating?
18 If this were true, we would believe that
19 the patients being withdrawn because of an adverse
20 event to have fared poorly during the continued
21 follow-up. However this was not the case.
22 This slide shows the time to initiation of

1 treatment with epoprostenol in patients withdrawn
2 because of clinical deterioration compared to those
3 withdrawn because of an adverse event. Epoprostenol
4 was instituted emergently in patients who were
5 withdrawn during this study because of a clinical
6 deterioration, whereas in the group withdrawn because
7 of an adverse event, epoprostenol was generally
8 started electively as a substitute for treprostinil.
9 Within two weeks of withdrawal of the
10 study, epoprostenol therapy was instituted in nearly
11 75 percent of the patients withdrawn because of
12 clinical deterioration, but only about 20 percent of
13 the patients were withdrawn because of an adverse
14 event, specifically infusion site pain.
15 This slide shows the time of death in
16 patients withdrawn because of clinical deterioration
17 and those withdrawn because of an adverse event. I
18 want to note that these data have just been analyzed
19 and have not been presented to the FDA.
20 After one year, none of the patients who
21 withdrew because of an adverse event had died as
22 compared with nearly 50 percent of the patients who

1 withdrew because of clinical progression of the
2 disease.
3 These observations indicate that patients
4 who withdrew for an adverse event were distinctly
5 different than those who withdrew because of clinical
6 deterioration, thus supporting our prespecified
7 statistical plan to analyze these two groups of
8 patients differently.
9 Of course, one could argue that perhaps
10 only some of the patients who withdrew because of an
11 adverse event have misclassified, and in fact, the FDA
12 reviewer has suggested a variety of ways by which
13 varying numbers of patients could be reassigned from
14 the group that withdrew because of an adverse event to
15 the group that withdrew for clinical deterioration.
16 This slide lists three of those proposed
17 alternate definitions. Approach one includes
18 reassignment of patients who died or are transplanted
19 within 100 days of randomization.
20 Approach two adds patients who received
21 epoprostenol within 30 days of discontinuation.
22 And approach three expands this

1 reassignment to patients who received epoprostenol
2 within 100 days of randomization.
3 Regardless of the approach used for these
4 post hoc reassignments, a treatment effect of
5 treprostinil could still be demonstrated with respect
6 to their prespecified primary and secondary endpoints.
7 Now I'd like to focus on the second issue
8 raised by the FDA review, the clinical meaningfulness
9 of the finding of a treatment effect and how we
10 address this issue.
11 This is an interesting issue because no
12 criteria have been established to determine what
13 increase in walk distance should be considered
14 clinically meaningful. We know that between group
15 differences in six minute walk distance in placebo
16 controlled trials with effective drugs in heart
17 failure and pulmonary hypertension have averaged about
18 25 meters and that this magnitude of treatment effect
19 has generally been regarded as clinically relevant.
20 Larger increases as six minute walk
21 distances have been observed, but only in open label
22 studies. Nevertheless, it's possible to consider a

1 wide variety of criteria to define a clinical
2 responder, including improvements greater than or less
3 than 20 to 25 meters.
4 This slide shows cumulative frequency
5 distribution curves for the six minute walk test with
6 various criteria for a clinical responder plotted on
7 the X axis and percent of patients meeting the
8 response on the Y axis.
9 Regardless of the criteria used to define
10 a clinical responder, this graph shows that clinical
11 responders were always more common in the treprostinil
12 group than in the placebo group and that the magnitude
13 of the difference in favor of treprostinil did not
14 depend on the definition used to define clinical
15 response.
16 I'd also like to note that in studies with
17 treprostinil, as was the case with epoprostenol, the
18 severity of exercise intolerance is a major
19 determinant of the ability of drugs to improve
20 exercise tolerance. This slide shows the relation
21 between baseline six minute walk tests and the
22 magnitude of benefit associated with the use of

1 treprostinil.

2 The sicker the patient, the more limited

3 their baseline exercise capacity, the greater the

4 improvement produced by treprostinil.

5 Similarly, the more advanced the

6 functional class at baseline, the greater the

7 improvement in a six minute walk distance produced by

8 treprostinil.

9 These findings are noteworthy since

10 earlier studies in patients with pulmonary arterial

11 hypertension largely excluded patients with Class II

12 symptoms.

13 Another way of assessing clinical

14 meaningfulness is not to look only at single

15 variables, but to look at the totality of the data

16 available for review and analysis. First, let's look

17 at the totality of the data available from the six

18 minute walk test.

19 Remember that exercise tolerance during

20 the six minute walk test was evaluated not only by the

21 distance traversed, but also by the symptoms

22 experienced by the patient during the test. This

1 slide shows the difference in Borg dyspnea score from
2 baseline to week 12 in the treprostinil-placebo groups
3 for the two studies individually and combined.
4 In both Studies 04 and 05, treprostinil
5 was associated with less severe symptoms, and the
6 magnitude of the treatment was remarkably similar.
7 The differences in both trials were highly
8 significant.
9 This is important because the intent of
10 the six minute walk test is to determine how much
11 patients can do during the course of daily activities.
12 Yet the capacity of patients to function is determined
13 not only by what they can do when they exert
14 themselves, but also how they feel when they are
15 carrying out their activities.
16 Two patients, for example, may show an
17 equal ability to walk down the street, but their
18 clinical status is not equal if one walks with ease
19 and the other walks while huffing and puffing.
20 Similarly, in the absence of any new
21 treatment, it is possible for patients to walk longer
22 during an exercise treatment simply because they're

1 more motivated, and this should be accompanied by more
2 symptoms, not less symptoms.
3 It is, therefore, important not only to
4 look at the distance traversed during the six minute
5 walk, but also the symptoms experienced during the
6 walk. This was recognized by the investigators and
7 the sponsors when Studies 04 and 05 were designed,
8 which is why the protocol specified that both distance
9 and symptoms were to be assessed during the six minute
10 walk test.
11 These data indicate that patients in the
12 treprostinil group experienced less symptoms even
13 though they walked for a longer time than patients in
14 the placebo group.
15 This point is illustrated graphically on
16 this slide. During the course of Studies 04 and 05,
17 patients in the treprostinil group not only
18 experienced a progressive increase in the distance
19 traversed, but also a progressive decrease in the
20 symptoms experienced during the six minute walk test.
21 To determine if patients who had an
22 increase in their walk distance were the same as those

1 who had a decrease in their symptoms, we plotted
2 cumulative frequency distribution curves which combine
3 the ranks of the distance response with the ranks of
4 the symptoms response in individual patients.
5 Patients who had an improvement in both
6 distance and symptoms were assigned the highest rank.
7 Those with an improvement in one, but a deterioration
8 in the other were assigned middle ranks, and those
9 with a deterioration in both were assigned the lowest
10 rank.
11 Shown on the X axis is a distribution of
12 combined ranks from lowest to highest, and shown on
13 the Y axis is the proportion of patients achieving a
14 given combined rank or better.
15 At week one, the difference between the
16 two treatment groups was small. At week six, the
17 separation between the two treatment groups became
18 more apparent, and even more apparent at week 12.
19 These graphs confirm the hypothesis that
20 if we consider all aspects of exercise tolerance, a
21 much larger proportion of patients benefitted from
22 treatment with treprostinil than could be envisioned

1 based on analysis of walk distance alone.

2 Finally, let's look not only at the

3 totality of the data from the walk test, but the

4 totality of the data available from all measures of

5 efficacy evaluated in the trials.

6 Remember that there was not only a primary

7 endpoint in the two pivotal trials, but there were

8 secondary endpoints which were specifically designed

9 to provide a more complete picture of the effective of

10 treprostinil on exercise. This is important since

11 patients with pulmonary hypertension are not just

12 symptomatic during exercise. They are disabled

13 throughout the day.

14 In Studies 04 and 05, investigators were

15 asked to record the appearance or resolution of each

16 of eight symptoms and eight signs of pulmonary

17 hypertension and the statistical plan specified that

18 these changes were to be combined into a single

19 composite score.

20 As you can see, treprostinil produced

21 significant improvements in this composite score. The

22 magnitude of the improvement was remarkably similar in

1 the two trials and was highly significant.

2 We recognize that the use of the composite

3 score, although prespecified in the statistical plan,

4 represents an arbitrary approach to the analysis of

5 these data since the approach assumes that all eight

6 symptoms and all eight signs have the same clinical

7 weight.

8 To address this concern, we evaluated the

9 effect of treatment on individual symptoms across the

10 two trials. This slide shows the number of patients

11 in the placebo and treprostinil groups in whom

12 symptoms reported at baseline resolved completely on

13 the left or in whom symptoms not present at baseline

14 developed during the 12-week study on the right.

15 According to the protocol, the baseline

16 period was defined as the four weeks prior to

17 randomization. As you can see, as compared with the

18 placebo group, patients in the treprostinil group were

19 more likely to have symptoms resolved complete and

20 were less likely to have symptoms develop during the

21 12 week study period.

22 For example, if you take chest pain,

1 that's third from the top. Chest pain resolved
2 completely in 25 treprostinil patients, but in only 17
3 placebo patients and was newly reported in 50 placebo
4 patients, but in only 24 treprostinil patients.
5 A similar pattern was seen for most all
6 other symptoms. As expected, if you look at dyspnea,
7 we observed little change in dyspnea since nearly all
8 patients had dyspnea at baseline, and dyspnea,
9 although improved, continued to be reported during
10 treatment.
11 Now, we recognize that there are two
12 possible limitations to this analysis. First, the
13 time periods we compare are not of equal duration.
14 The baseline period is four weeks long, whereas the
15 study period is 12 weeks long.
16 Second, we have already seen data
17 suggesting that the effect of treprostinil increases
18 with time. As a result, it may take time for the drug
19 to exert a full effect on the symptoms of pulmonary
20 hypertension.
21 To address these two concerns, we carried
22 out initial analysis that compared symptoms reported

1 during the last six weeks of the double blind therapy
2 with symptoms reported during the four weeks prior to
3 randomization.
4 Once again, as compared with the placebo
5 group, patients in the treprostinil group were more
6 likely to have symptoms resolve completely and were
7 less likely to have symptoms develop during the 12
8 week study period.
9 Again, taking chest pain as an example,
10 chest pain resolved completely in 48 treprostinil
11 patients, but in only 37 placebo patients and was
12 newly reported in 30 placebo patients, but only in
13 eight treprostinil patients.
14 A similar pattern was seen for most of the
15 other symptoms.
16 We'd like to point out that a four week
17 baseline observation period is appropriate for most of
18 the symptoms on this slide with a possible exception
19 of syncope, which we recognize can be an infrequent
20 event.
21 We also understand that whereas many of
22 the symptoms we evaluated represent subjective

1 sensations, syncope represents a true clinical event.
2 Hence, we carried out an additional analysis focused
3 on syncope given its special importance.
4 This slide shows the number of patients in
5 the placebo and treprostinil groups in whom syncope
6 reported at baseline resolved completely or in whom
7 syncope not previously reported at baseline was
8 observed during the study.
9 Three different analyses are presented
10 based on how one defines the baseline period or the on
11 treatment period. The first analysis compares the
12 last six weeks of double blind therapy with the four
13 weeks prior to randomization.
14 The second analysis compares the entire 12
15 week double blind period with the four weeks prior to
16 randomization.
17 And the third analysis compares the entire
18 12 week double blind period with any history prior to
19 randomization.
20 Regardless of the definition, as compared
21 with the placebo group, patients in the treprostinil
22 group were more likely to have previously reported

1 syncope resolved completely and were less likely to
2 have syncope develop during the study period. These
3 results are consistent across all three analyses.
4 The second principal reinforcing endpoint
5 was the dyspnea-fatigue rating. Treatment with
6 treprostinil produced a significant improvement in the
7 dyspnea-fatigue rating at week 12. The magnitude of
8 the improvement was remarkably similar in the two
9 trials and was highly significant.
10 The effect of treprostinil on the
11 magnitude of task component of the dyspnea-fatigue
12 rating is shown on this slide. When compared with
13 placebo, treprostinil patients were more likely to
14 experience improvement in this measure, 40 percent on
15 treatment versus 15 percent on placebo; were less
16 likely to experience deterioration, five percent on
17 treatment versus 19 percent on placebo.
18 Since the magnitude of task component
19 parallels the patient's New York Heart Association
20 functional class, these treatment differences reflect
21 changes that would generally be considered to be
22 clinically relevant.

1 The third principal reinforcing endpoint
2 was the combined risk of death within 12 weeks or
3 transmutation or clinical deterioration leading to
4 withdrawal from the study and requiring intravenous
5 rescue therapy. This endpoint was proposed by the FDA
6 even though it was recognized that the trial did not
7 have sufficient power to evaluate a treatment effect
8 on this endpoint.
9 The definition used for this endpoint was
10 prespecified in the statistical analysis plan, agreed
11 to with the FDA before the code was broken. There
12 were 16 such patients in the placebo group and 13 in
13 the treprostinil group. This difference was not
14 statistically significant.
15 I'd like to explore, however, if the lack
16 of statistical significance reflects the lack of a
17 true treatment effect, the small number of events, or
18 the definition used to defined clinical worsening.
19 We addressed the last possibility by
20 asking whether there were patients in the trials who
21 deteriorated clinically, but who did not die or get
22 transplanted or require rescue therapy. There were

1 seven patients whose condition deteriorated so much
2 that they required hospitalization specifically for
3 the treatment of worsening pulmonary hypertension or
4 right heart failure, but who did not fulfill other
5 criteria for clinical worsening.
6 Six of these were in the placebo group,
7 and one was in the treprostinil group.
8 In addition, there were eight patients
9 whose condition deteriorated so much that they were
10 considered too ill to undergo an exercise evaluation.
11 All of these patients were prospectively assigned to
12 worst rank in the evaluation of exercise tolerance.
13 Six of these were in the placebo group,
14 and two were in the treprostinil group. If we now
15 were to include these 15 patients who deteriorated
16 clinically in our definition of clinical worsening.
17 Then there would be 28 patients in the placebo group,
18 but on 16 in the treprostinil group.
19 According to our prespecified approach,
20 treprostinil therapy was associated with a 19 percent
21 reduction in risk, but if we use an expanded
22 definition, which was not prespecified, treprostinil

1 therapy was associated with a 45 percent reduction in
2 risk.
3 Given its post hoc nature, this new
4 analysis does not allow for any conclusions, but it
5 does provide comfort that treprostinil may be
6 favorably influencing the clinical course of these
7 patients.
8 Additional support for this hypothesis
9 comes from an analysis of hospitalizations in Studies
10 04 and 05. This study shows the number of patients
11 who were hospitalized and the total number of
12 hospitalizations for any reason for worsening
13 pulmonary hypertension or right heart failure or any
14 other reason.
15 The columns under the number of patients
16 do not add up because a few patients were hospitalized
17 for worsening pulmonary hypertension and for another
18 reason at different times during the study.
19 There were a total of 75 patients who were
20 hospitalized 107 times for any reason. Thirty-eight
21 patients in the placebo group were hospitalized 54
22 times, and 37 patients in the treprostinil group were

1 hospitalized 53 times.

2 However, if we look specifically at the
3 hospitalizations for worsening pulmonary hypertension
4 or right heart failure, there were 18 patients in the
5 placebo group, but only seven in the treprostinil were
6 hospitalized at least once.

7 These patients were hospitalized a total
8 of 22 times in the placebo group, but only eight times
9 in the treprostinil group for worsening pulmonary
10 hypertension or right heart failure.

11 Now, please note that there is a small
12 excess of hospitalizations for other reasons in the
13 treprostinil group. This excess appears to largely be
14 due to the fact that some patients were hospitalized
15 for the management of a variety of miscellaneous
16 reasons that were neither cardiac nor pulmonary in
17 origin.

18 Nevertheless, the reductions in
19 hospitalizations for pulmonary hypertension or right
20 heart failure in the treprostinil group is striking
21 and further supports the hypothesis that treprostinil
22 favorably influences the clinical course of patients

1 with pulmonary arterial hypertension.

2 Finally, I'd like to mention briefly the
3 effect of treprostinil on hemodynamics and quality of
4 life, even though neither was a primary or principal
5 reinforcing endpoint. This slide summarizes the
6 changes in hemodynamic variables in treprostinil-
7 placebo groups after 12 weeks. Treprostinil was
8 accompanied by favorable hemodynamic effects as might
9 be expected for an effective drug for the treatment of
10 pulmonary arterial hypertension with minimal changes
11 in blood pressure or heart rate.

12 Quality of life was measured by the
13 Minnesota Living with Heart Failure questionnaire, was
14 also measured in a subset of the patients in the
15 study. Treprostinil was accompanied by an improvement
16 in the physical domain, with little change in the
17 emotional component of the instrument.

18 Now, at the conclusions of Studies 03, 04,
19 and 05, each patient had an option of remaining on
20 treprostinil if they had been randomized to active
21 drug or initiating treprostinil if they had been
22 randomized to placebo. Ninety-five percent of the

1 patients assigned to treprostinil who completed 12
2 weeks of treatment elected to continue on open label
3 treatment with the drug.
4 In addition, following the end of
5 enrollment into the double blind trials, patients
6 could be enrolled directly into the open label study
7 on a compassionate basis.
8 As of October 2000, 631 patients had
9 entered the open label extension study, Study 06.
10 This is an impressive number, given the fact that
11 there are currently only about 3,000 patients
12 worldwide being treated with intravenous epoprostenol,
13 which has been commercially available for the
14 treatment of pulmonary hypertension for several years.
15 This slide summarizes pooled data on
16 exercise tolerance in Study 06. Shown is the number
17 of patients with an exercise test at each point in
18 time, the mean dose of the drug, and the change in
19 exercise performance during the six minute walk test.
20 It should be noted that all of the data in
21 this slide are collected in an open label manner.
22 Nevertheless, these data are consistent with the

1 hypothesis that the benefits of treprostinil are
2 maintained during long term treatment with the drug.
3 In summary, the administration of
4 subcutaneous treprostinil to patients with pulmonary
5 arterial hypertension results in consistent and
6 clinically meaningful improvements in a variety of
7 measures that reflect the impaired clinical status of
8 these patients. These measures include exercise
9 tolerance, both distance and symptoms; individual
10 symptoms, as well as composite symptom scores and
11 hemodynamic variables.
12 The improvement in these efficacy
13 parameters is comparable to that seen with other drugs
14 that have been shown to be effective in the treatment
15 of pulmonary hypertension and heart failure.
16 Thank you.
17 CHAIRMAN BORER: Thank you very much, Dr.
18 Rich. That was a very nice summary.
19 The committee I'm sure will have many
20 questions. While the chairs are being turned around,
21 let me just begin with one. One of the problems that
22 we will have to grapple with is the magnitude of the

1 clinical benefit associated with administration of the
2 drug.
3 You know, we heard two very compelling
4 statements by patients who have done quite well, and
5 I think that for me at least, because I don't see so
6 many patients with pulmonary hypertension, I need some
7 clarification from an expert like you.
8 In addition, because of issues completely
9 beyond your control or the sponsor's control, the
10 measures of drug effect that were used, the six minute
11 walk test, symptoms measures, what have you, are
12 associated with a fair amount of variability. So, you
13 know, it's hard to extrapolate from them to the issues
14 of day-to-day living.
15 Having said all that, we heard from two
16 people who seem to have improved rather dramatically,
17 but I don't have a good sense of the likelihood of
18 spontaneous remission or major spontaneous improvement
19 during the natural course of patients who have
20 pulmonary hypertension.
21 And your Slides 54 and 55 compounded that
22 confusion for me because so many patients on placebo

1 appear to have complete resolution of major symptoms
2 during the course of the study. Of course, that was
3 only during a 12 week study, and we're talking about
4 a process that goes on much longer than that.
5 And to take this just one step further,
6 you showed us median changes in walking time -- in
7 walking distance, rather, during six minutes, and
8 that's reasonable enough, but from the other material
9 received, it seems that the mean change even on drug
10 was actually slightly in the negative direction, but
11 more negative on placebo.
12 So it sounds like there's a fair amount of
13 variability here in patients who have primary
14 pulmonary hypertension. So I'd like to have a sense
15 of what the variability is, what people with this
16 disease can expect over time.
17 Could we have expected the kind of
18 dramatic improvements that we heard about from two
19 patients here in the absence of therapy? I mean,
20 what's the likelihood of that?
21 DR. RICH: Okay. That's actually three
22 questions. Let me kind of deal with them one at a

1 time.

2 First, in terms of, I guess, the natural
3 history question, there is no spontaneous resolution
4 of this disease. The only case report that was
5 published about 20 years ago was in a patient who
6 after the case report was published died of PPH.

7 I can tell you having treated this disease
8 for 21 years, I have never seen a patient get better
9 on their own, but you know, as with all cardiovascular
10 diseases, there's fluctuations. They'll tell you, "I
11 have good days and bad days," which is really
12 characteristic of the patients with pulmonary
13 hypertension for reasons we've never explained, and I
14 think every patient will testify that they have a lot
15 of good days and bad days, and as the treatment
16 becomes more effective, the good days start to
17 outweigh the bad days.

18 So it's not surprising to me that on any
19 given day that you might question a patient that they
20 will say, "You know, having less chest pain today,"
21 or, "I'm no longer dizzy," or, "I'm not longer having
22 leg swelling."

1 And you see them next week, and now
2 they're coming, telling you it's terrible. Things are
3 getting worse.
4 And so from the clinical perspective, I
5 wouldn't ever take one point in time to define the
6 patient's course. It really has to be a series of
7 points that define the course.
8 I think the noise that you're seeing
9 regarding the reporting of symptoms is characteristic
10 both of clinical trials where people on placebo report
11 they're feeling better because they're in a trial, and
12 some of the way the disease kind of fluctuates in
13 terms of the expression of symptoms on a day-to-day
14 basis.
15 I'll give you another example which is
16 kind of typical. The patients start to feel better.
17 They do more, and when they do more, they get more
18 symptoms, and so they'll tell you that, you know, "I'm
19 feeling great. So I decided now to go with my family
20 on a vacation, and when I came back, I was in bed for
21 three days. I was so exhausted because we decided to
22 do things I've never done before."

1 So how do you put a number score on that?
2 And so I think from my perspective, these data are
3 certainly consistent with the disease and the clinical
4 manifestation of the disease and clinical trials where
5 placebo patients oftentimes report an improvement even
6 though they're not on effective therapy.
7 Now, the other question you asked was?
8 CHAIRMAN BORER: One had to do with the
9 difference between the median improvement in walking
10 distance and the mean slight reduction and the
11 variability that that implies about the disease
12 process, the effect of the drug, what have you.
13 DR. RICH: Okay. I think I'm going to let
14 my statisticians give you a more articulate response
15 to that.
16 DR. KOCH: Gary Koch, Biostatistics
17 Department, University of North Carolina.
18 Could I have slide 44 or 44 from the main
19 presentation?
20 In these studies because of the way in
21 which data for those patients who died or had
22 transplantation or deteriorated were managed in terms

1 of assigning worst values, it becomes very difficult
2 to quantify the effect size in terms of traditional
3 values, like means or medians, particularly for means
4 because the mean requires you to average in some value
5 for these people that in some sense had no data.
6 The median is more straightforward in the
7 sense that you can put them at the bottom in terms of
8 a rank and then find a middle value. But the most
9 informative way to interpret the effect size or the
10 benefit is in terms of these Kaplan-Meier plots which
11 are shown behind you in slide 44.
12 And what you can do with these displays is
13 to identify potentially a goal for improvement in
14 walking distance, such as improving by at least 20
15 meters, and then note what fraction of patients in
16 each of the groups fulfills that criterion.
17 And in this particular case, it's around
18 42 percent in the treprostinil group and around 30
19 percent in the placebo group. So the difference is
20 about 12 percent.
21 And more or less throughout this
22 continuum, the vertical distance between the Kaplan-

1 Meier curves is about ten percent. So for any
2 particular status that one might identify as
3 favorable, about ten percent more of the patients in
4 the treprostinil group meet that goal compared to
5 counterparts in the placebo group.
6 Moreover, they achieve this benefit in
7 walk even though their Borg dyspnea scores show more
8 favorable improvement. That is, in doing this
9 increase in walk, they're actually exerting less
10 effort, and that is another thing that makes the data
11 for the walk more difficult to interpret because the
12 groups are different in terms of exertion.
13 The walking distance would be more
14 straightforward to interpret if each of the two groups
15 was providing a similar level of exertion, but on the
16 Borg dyspnea scores, the exertion required by those in
17 the treprostinil group was very significantly less
18 than that in the placebo group, and so that becomes a
19 confounding influence, and that makes the
20 interpretation of walk more difficult because actually
21 the treprostinil group is at a little bit of a
22 disadvantage there because the placebo people are

1 actually exerting themselves more, and that's why we
2 had the additional displays that integrated the
3 information from the Borg dyspnea score with that from
4 the walking distance.
5 CHAIRMAN BORER: Thank you.
6 Let's move on. Steve?
7 DR. NISSEN: Yes. Stuart, I had three
8 questions for you. I didn't see in here any analysis
9 of any differences between the primary pulmonary
10 hypertension population and those that were not
11 primary pulmonary hypertension. I'd like to have your
12 comment on that because I do think that has very
13 important potential implications for labeling.
14 I know that splitting a group that's small
15 has statistical problems associated with it, but I'd
16 like to know, first, let's do that one first.
17 DR. RICH: Okay. Well, we could show that
18 data. Why don't you show the -- do you want to see
19 just PPH alone or do you want --
20 DR. NISSEN: Yeah. I guess I'm trying to
21 get a sense for whether there was any differences in
22 response according to the underlying diagnosis.

1 DR. RICH: Okay. So these are PPH alone,
2 which is about 60 percent of the total group enrolled.
3 And this is the same display that we've shown
4 throughout the presentation. So the median six minute
5 walk is on top. This is the treprostinil-placebo
6 group and the p value. These are the secondary
7 primary enforcing endpoints here, their differences,
8 and the p values.
9 This is death, transplant, rescue. No
10 difference. Hemodynamic changes, and then quality of
11 life.
12 DR. NISSEN: And then could we see the
13 group that doesn't have PPH?
14 DR. RICH: Well, we actually don't -- do
15 we have a combined? I think we have them by
16 diagnosis. So we have general heart disease
17 separately and connective tissue disease separately.
18 Is that okay?
19 DR. NISSEN: Yeah, please.
20 DR. RICH: Okay. So this is the
21 connective tissue disease group. Again, this is the
22 median walk, differences. Borg dyspnea scores,

1 fatigue ratings, et cetera, the difference between the
2 groups.
3 Hemodynamic differences and quality of
4 life.
5 Okay, and then the general heart disease
6 group referred to as "Eisemingers (phonetic)," which
7 is actually what they really were.
8 Change in walk, change in symptoms, change
9 in hemodynamics, quality of life.
10 DR. NISSEN: That's very helpful.
11 DR. RICH: No difference in change of walk
12 for this subset. That's correct.
13 DR. NISSEN: Right. Okay. Now, my second
14 question --
15 DR. FLEMING: Can we go back to the PPH?
16 DR. RICH: The PPH, can we put that back
17 up again?
18 DR. FLEMING: So this is from the pooled
19 studies?
20 DR. RICH: Yes.
21 DR. FLEMING: What are the n's? Could you
22 clarify the n's?

1 DR. RICH: Wider variable. It's variable
2 because not every patient ended up having each of
3 these determinations made. For example, if a patient
4 died before 12 weeks, then we don't have hemodynamic
5 data. So that's why there's --
6 DR. FLEMING: So what are the n's for the
7 six minute walk?
8 DR. RICH: The n's for the six minute
9 walk.
10 DR. KOCH: Gary Koch.
11 If my understanding is correct, the n's
12 for the six minute walk would be the larger numbers
13 because the six minute walk was always analyzed on an
14 intent to treat basis.
15 Is that correct, Carl?
16 DR. ANDERSON: Yes, that's correct.
17 DR. KOCH: And the n's for the other
18 outcomes would be the number of patients who provided
19 data on those outcomes because the original analysis
20 plan on the other outcomes would basically only use
21 the people that had data for those.
22 Carl, did you want to clarify any further?

1 DR. ARNISON: Yes. Carl Arnison
2 (phonetic) from United Therapeutics.
3 He got the description right.
4 DR. FLEMING: And this is by the sponsor
5 number one definition criterion?
6 DR. RICH: Well, this would be the
7 investigator on reporting --
8 DR. FLEMING: This is for sponsor number
9 one? This is comparable to the same criterion you
10 used in your primary analysis?
11 DR. RICH: yes.
12 DR. FLEMING: And were any of the patients
13 who had death, transplantation, or discontinuation for
14 worsening disease in this subgroup?
15 DR. RICH: Yes.
16 DR. FLEMING: And why then is the adjusted
17 analysis or FDA analysis number one when you account
18 for those patients rather than censoring? Have you
19 computed that analysis?
20 DR. KOCH: He wants to know if we do
21 analysis one, two, and three.
22 DR. FLEMING: On just this subset.

1 DR. ARNISON: On just this subset you're
2 asking?
3 DR. FLEMING: Right.
4 DR. ARNISON: I don't think we have that
5 one available for just PPH.
6 DR. NISSEN: My second question, Stuart,
7 may be a little bit more difficult one, but in
8 preparing for this I reread some of the literature
9 here, and I read the New England Journal paper, which
10 you're one of the authors of with respect to
11 epoprostenol, and I noted that between placebo and the
12 treatment group, there was a 60 meter difference in
13 the same six minute walk test with about the same
14 baseline characteristics.
15 And we have 16 meters in this combined
16 study. Does that suggest that treprostinil has a
17 lower efficacy therapy? And it's very important for
18 me to understand. Is, in fact, this a lower efficacy
19 therapy than epoprostenol based upon at least the six
20 minute walk test?
21 DR. RICH: Can I ask you which of the New
22 England Journal papers you're referring to?

1 DR. NISSEN: Well, it was a 1996
2 manuscript.
3 DR. RICH: The '96. So that would be the
4 summary of the randomized clinical trial.
5 DR. NISSEN: Yeah.
6 DR. RICH: Okay. Well, there were some
7 important differences in the conduct of those study
8 and differences why that result may not be surprising.
9 First of all, those were PPH patients
10 only, and I say that because if you notice, the
11 congenital heart disease group tends to have a
12 different kind of response to epoprostenol than the
13 PPH.
14 Secondly, they were really limited to
15 Class III(b) and IV. They were really quite ill
16 patients, and what we observed in the treprostinil
17 group is that the sicker you were, whether it's by
18 baseline Heart Association class or baseline walk,
19 which was much lower in that group, the improvement
20 was greater.
21 And then thirdly was an open label study.
22 There was no blinding at all.

1 So I can't really tell you whether this is
2 a less effective therapy. I can tell you it's a
3 comparable therapy, but trying to compare these two
4 trials is going to be difficult because of those very
5 distinct reasons.
6 DR. NISSEN: But the baseline walk times
7 were about the same in the two?
8 DR. RICH: No, they were significantly
9 lower. The baseline walk was lower in the Flolan
10 study than it was in this one.
11 DR. NISSEN: It's about 300 meters.
12 DR. RICH: I thought it was 276.
13 DR. NISSEN: Okay. Well, my reading was
14 pretty close. Okay. Well, I'm just trying to get a
15 sense for that.
16 And then the third point, I guess, would
17 be the lack of efficacy in the more mild disease
18 patients. It was really pretty striking here with
19 treprostinil, and obviously this has a lot of impact
20 on the thinking because it would seem to me that a
21 less invasive therapy would be an ideal therapy to
22 initiate in a patient at an earlier stage in their

1 disease, you know.

2 And so the tendency would be for the

3 clinicians to want to use treprostinil early in the

4 disease because they don't have to go to all of the

5 lengths that they have to go to for epoprostenol, and

6 yet in those early disease patients there was a rather

7 striking lack of efficacy here.

8 I would like your comments about that.

9 DR. RICH: Yeah, and I have to tell you

10 honestly we anticipated that, and the reason is

11 because the efficacy measure that you're referring to

12 is exclusively walk distance. It's not any of the

13 other secondary endpoints, which in fact, were very

14 significant even in the Class II patients.

15 If you think about the definition of a

16 Class II patient, it's a patient who only has symptoms

17 upon more than normal exertion. So what they're

18 telling you is that walking six minutes at their own

19 pace gives them no symptoms, and so the likelihood of

20 getting that subset to walk a whole lot farther, they

21 would either have to push the symptoms, which they

22 don't want to do, or they would walk at the same pace

1 and say, you know, this is the result.

2 So at least from my perspective, this is

3 not a surprising finding. But if you look at the

4 totality of the assessment of these patients because

5 they're not symptom free, I mean, they're coming to us

6 because they are symptomatic with a lot of other types

7 of symptoms. Those improved very considerably.

8 This is broken down just by class at

9 baseline. So, again, the same display starting with

10 the primary endpoint, median six minute walk on top.

11 And you're right. The difference is not striking.

12 And then looking at changes in the

13 secondary endpoints, hemodynamics and quality of life

14 measures.

15 CHAIRMAN BORER: JoAnn.

16 DR. LINDENFELD: I have just a couple of

17 questions about the pain medications these patients

18 were using. Was any attempt made to standardize the

19 use of pain medications around the time of exercise

20 testing or assessment of the fatigue index?

21 DR. RICH: No.

22 DR. LINDENFELD: And can you tell me what

1 effect narcotics have on exercise time and assessment
2 of dyspnea?
3 DR. RICH: I can do that. It's actually
4 part of the safety presentation. If you'd like me to
5 do it, I can or Dr. Barst can do it when she does it.
6 DR. LINDENFELD: I can wait.
7 DR. RICH: Okay. Yes.
8 DR. BREM: I noticed in your presentation
9 on slide 65 that there seems to be a progressive
10 increase in dose, and in the narrative materials that
11 were provided there was a suggestion of tolerance to
12 this medication over time.
13 Would you comment on that, tolerance and
14 perhaps tachyphylaxis and, therefore, lack of efficacy
15 later on?
16 DR. RICH: Yeah. I know that's come up,
17 and first is the issue of how we are defining
18 tolerance. Are we defining tolerance is that lack of
19 efficacy at the same dose or are we defining tolerance
20 as requiring more medication to achieve the same
21 effect?
22 And I have to say that we really can't

1 prove or disprove that concept from the conduct of
2 this trial because that really was not a goal to try
3 to determine that.
4 If you look at this, which was open label
5 use in 06, what you're seeing is a fourfold increase
6 in the mean dose of the patients over time and about
7 a fourfold increase in their performance based on a
8 six minute walk.
9 In our experience with epoprostenol, and
10 a lot of what we do have really been judged by that
11 experience, most of us would take about six months to
12 a year to reach what we would call an ideal dose,
13 namely, that if you go up too quickly, you get a lot
14 of the prostecycline (phonetic) side effect of
15 flushing and headache, and the patients are unhappy.
16 But if you can tiptoe your way up, then they tolerate
17 that so much better and continue to improve.
18 And so we assumed, rightly or wrongly,
19 that the same strategy would need to be used in these
20 patients, and so the investigators were encouraged to
21 follow the same strategy after the randomized trial
22 was over, namely, continue to increase the dose in

1 patients who report symptoms and have acceptable side
2 effects.
3 And so I think what you're just seeing
4 here is that strategy, and I wouldn't want to make a
5 claim for or against tolerance. I can tell you
6 anecdotally in my own experience with epoprostenol
7 there is no tolerance to the drug. Most of my
8 patients achieve a dose which no longer has to be
9 changed from that point on. I'm doing this for 11
10 years with them.
11 I don't want to use one of the patients
12 here, but a patient here told you that she also
13 achieved a dose which no longer had to be changed, and
14 that is characteristic, but we generally don't reach
15 it in 12 weeks.
16 CHAIRMAN BORER: Tom and then Paul.
17 DR. FLEMING: Can you explain in this --
18 can you put that slide back up?
19 DR. RICH: Sure.
20 DR. FLEMING: Are you interpreting this
21 slide to provide substantial evidence that you're
22 going to have maybe a 55 meter increase if you follow

1 out to 21 months?

2 DR. RICH: No. All I'm saying is that

3 you can continue to see benefit over time.

4 DR. FLEMING: You're interpreting that

5 based on what looks to be 80 to 90 percent missing

6 information.

7 DR. RICH: Well, I mean --

8 DR. FLEMING: This is an incredibly

9 inadequate follow-up to say anything meaningful.

10 Would you not agree past the first few months?

11 DR. KOCH: Gary Koch, Biostatistics, North

12 Carolina.

13 My understanding is that this is an open

14 label safety study that has patients entered

15 consecutively as they become identifiable. This is

16 not a study that was designed to prove efficacy.

17 I believe that the only point here is that

18 among those individuals that have data further out in

19 time and also have dose changes as described, there

20 appears to be continued benefit. I don't think any

21 other point is being made about it.

22 And it certainly is not an attempt to

1 prove any kind of efficacy.

2 DR. FLEMING: Well, as you had said, Gary,

3 and this is certainly the case, this is an open label

4 study. It is, in fact, in no way capable of providing

5 us anything really meaningful or interpretable about

6 efficacy.

7 And so even being able to say this is

8 evidence of continued benefit, I'm not sure what that

9 means in terms of continued benefit, but clearly a

10 study such as this is not going to give us anything

11 remotely reliable about long-term effects. We would

12 need to be following a large fraction of people.

13 I have no clue whether the people who were

14 having difficulties are the very people who are less

15 likely to continue on or to join the open label study.

16 DR. KOCH: I think the main point on this

17 particular slide is that the individuals who have

18 provided data at these further out points in time are

19 not doing atrociously, and so this is simply to --

20 DR. FLEMING: The essence of what I want

21 to know is in a cohort of patients provided this

22 intervention, what will be the long-term effect?

1 DR. KOCH: And that requires a long-term
2 efficacy study, but in this clinical area, 12 week
3 studies have been considered to be the usual way of
4 assessing efficacy in a double blind, placebo
5 controlled study.
6 DR. FLEMING: And these aren't 12 week
7 studies.
8 DR. KOCH: This is long-term safety data
9 where information on benefit has been collected and is
10 being reported for completeness of documentation.
11 CHAIRMAN BORER: Paul and then Ray.
12 DR. ARMSTRONG: I really have two
13 questions for Dr. Rich, the first fairly
14 straightforward and the second a little more
15 complicated.
16 Dr. Rich, in heart failures, you know, we
17 recognize that anti-inflammatory medications may
18 exacerbate that process through interference with
19 prostaglandins. What is the knowledge base in
20 pulmonary hypertension and how does that influence the
21 prescribing of anti-inflammatory medicines for these
22 patients?

1 DR. RICH: Are you referring to non-
2 steroidals or steroids?
3 DR. ARMSTRONG: An indomethacin, for
4 example, yes.
5 DR. RICH: Okay. There were some very
6 simplistic, small number of patient studies looking at
7 influence of both steroids and non-steroidals on PPH
8 published about 15 years ago, very uncontrolled. No
9 conclusions were drawn.
10 I think the wisdom is that they don't
11 impact the disease one way or the other. We do have
12 data about the use of the pain medications in this
13 trial in the safety presentation, and if you would let
14 Dr. Barst show that with you, I think she can show you
15 that.
16 But basically we did not see any influence
17 -- I'll let her show you the date -- of any of the
18 pain medications used, whether it was the narcotics or
19 the non-narcotics, on the outcome measures.
20 DR. ARMSTRONG: If that's going to come up
21 in the safety part, that's fine. We'll wait for it.
22 The second question. The intersection

1 between adverse events and efficacy in this
2 presentation is complicated, and you've gone to some
3 length to provide new information on the consequences,
4 the clinical consequences following withdrawal for
5 adverse effects in your presentation. I want to
6 pursue that along a couple of lines, if I could, Mr.
7 Chairman.
8 The first is the distance between the
9 adverse events and the last measured efficacy since
10 that's an issue of controversy vis-a-vis how we
11 interpret the data. So the first question is the
12 temporal association between adverse events leading to
13 withdrawal and last documented efficacy measurement.
14 The second is the decision to withdraw a
15 patient from a trial like this is, as we all
16 recognize, complicated. The interface between the
17 physician, investigator, and the patient, as we heard
18 from some of the eloquent testimonies this morning,
19 some patients live through their adversity because of
20 perception of enhanced efficacy, which I take was not
21 the case in the patients who were withdrawn from this
22 study.

1 The third issue is that sometimes these
2 adverse events are clustered amongst different
3 institutions or investigators, and I wonder if you
4 could give us a little more insight into this since it
5 seems to cut at some of the central issues.
6 DR. RICH: Okay. So I guess there are
7 three questions. I'm working backwards.
8 Do we have by institution data on
9 withdrawal? Was it clustered to small issues? Do we
10 know this?
11 I don't think that was recorded.
12 The second --
13 CHAIRMAN BORER: Use a microphone, if you
14 will, please, for the record.
15 DR. ARNISON: We don't have the data, but
16 it's not our sense that there's a single center
17 driving the withdrawal rate.
18 DR. RICH: There are reporting centers,
19 but there are only 18 withdrawing from side effects.
20 So it's going to be less on average than one percent.
21 Your second question had to do with?
22 DR. ARMSTRONG: The issue of the time from

1 last measurement of efficacy that's the principal
2 endpoint. There's controversy on how to interpret
3 this, and I'm trying to elucidate in my own mind how
4 to make a judgment on that, and one impact would be
5 how close in time the withdrawal was to the last
6 measured efficacy.
7 And it may have been in the documentation
8 and I missed it, but I --
9 DR. RICH: We have that data, do we not,
10 Carl? We can show that.
11 Okay. So this is a plot of time to
12 continuation, and what I'd like to just point out is
13 remember that there were visits at weeks one, six, and
14 12. So the apparently sudden drop around week six is
15 coordinated with the time that the patient would come
16 to be assessed by the physician, and then at week 12.
17 DR. ARMSTRONG: I should be wider, but I'm
18 not sure that I am. Are you saying that -- what's the
19 distance?
20 DR. ARNISON: Okay. The distance isn't
21 actually depicted on this plot.
22 DR. ARMSTRONG: Okay. That was the

1 question.

2 DR. ARNISON: Just the time. Okay. The

3 distances themselves I don't think we have available

4 right now, but we did look at it, and there was no --

5 they basically looked like, you know, a varied

6 distribution, about the same way that the overall data

7 were distributed.

8 Some were doing slightly better; some were

9 doing slightly worse at the time of discontinuation,

10 and there wasn't any discernable pattern to it.

11 CHAIRMAN BORER: Okay. Ray and then Alan.

12 DR. LIPICKY: On clarifying this, do you

13 have information on how many patients had the week one

14 value carried forward and how many had the week sick

15 value carried forward? That might be a way of trying

16 to help with that question or you could look it up.

17 DR. RICH: We didn't make a slide with

18 that data, but that data has been provided.

19 DR. LIPICKY: I think I have two

20 questions, but maybe only one. Retrospectively, would

21 you say the six minute walk test was a lousy test to

22 have picked as a primary endpoint?

1 DR. RICH: It's a good question.
2 Retrospectively, you know, I have to tell you that
3 participating in this was a learning experience for me
4 as well. The standard is for the agency to require
5 a --
6 DR. LIPICKY: No, no, no. Just don't tell
7 me about the agency. I mean if it was a good thing or
8 a bad thing.
9 DR. RICH: Well, it's not so easy to
10 answer, Ray, and let me just tell you my thoughts
11 about this is we're required to pick a single measure
12 and say this is the primary endpoint, and that measure
13 is selected hopefully to represent whatever we're
14 trying to treat.
15 And so if the measure is lowering
16 cholesterol because I have an agent that I'm
17 purporting to lower cholesterol, the measure is
18 simple.
19 When the measure is treating people with
20 pulmonary hypertension, and especially once we expand
21 it not to just primary, but the primaries and the
22 collagen vascular diseases and the congenital heart

1 diseases, all of which have very unique signs and
2 symptoms, et cetera.
3 And when there are disease manifest in so
4 many ways, then I think choosing a single endpoint
5 like six minute walk distance is a little unrealistic
6 because as the other analysis showed, there were so
7 many other changes to the patient's benefit in the
8 secondary measures that patients come in and tell me
9 they feel better, which is the question I ask them
10 when I see them. "How do you feel?"
11 And if they say, "I feel so much better.
12 I could now walk without being helped from the waiting
13 room to your office," we may not be able to measure
14 that in the clinical trial, but that is a meaningful
15 benefit.
16 And so I think in retrospect what I would
17 probably suggest in future trials at least with
18 pulmonary hypertension, and maybe this can be expanded
19 even further, is a composite measure that tries to
20 incorporate a realistic measure of the disease
21 expression and not just a single element of the
22 disease.

1 DR. LIPICKY: Right, and I guess there is
2 a second question that is a correlate to that. It was
3 clear that shortness of breath was not the limiting
4 factor for exercise. The Borg dyspnea score was not
5 very high at the end of exercise. What is it that
6 limits exercise capacity in people with pulmonary
7 hypertension?
8 DR. RICH: Well, or what is it that limits
9 the distance someone walks in a six minute walk test,
10 which is another way to say that.
11 DR. LIPICKY: Yes.
12 DR. RICH: Because I think part of the
13 problem with the six minute walk test, which is not my
14 favorite test, is that people tend to walk in large
15 part by their style. You and I can walk down the
16 street, and I'll beat you every time because I'm a
17 fast walker and you're a slow walker, and yet when
18 we're --
19 DR. LIPICKY: How did you know that?
20 (Laughter.)
21 DR. RICH: And so I'm going to try, if I'm
22 limited, I'm going to try to improve myself to what my