

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE

+ + + + +

93rd MEETING

+ + + + +

Friday, August 10, 2001

+ + + + +

The committee met in the Jack Masur Auditorium, at Building 10, 9000 Rockville Pike, at 8:30 a.m., Jeffrey Borer, M.D. presiding.

PRESENT:

JEFFREY BORER, M.C., Acting Chair

JOAN C. STANDAERT, Executive Secretary

MICHAEL E. ARTMAN, M.D., Member

THOMAS FLEMING, Ph.D., Member

ALAN T. HIRSCH, M.D., Member

JOANN LINDENFELD, M.D. Member

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ORIGINAL

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ALSO PRESENT:

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

PAUL ARMSTRONG, M.D., Member

GLORIA ANDERSON, Ph.D., Guest

ANDREW S. BREM, M.D., Guest

ROBERT TEMPLE, Guest

RAY LIPICKY, M.D. Guest

PRESENTERS:

ISAAC KORBIN, M.D.

WILLIS MADDREY, M.D.

LEWIS RUBIN, M.D.

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A-G-E-N-D-A

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Acting Chair

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STANDAERT, Executive Secretary

Meeting open for public comment:

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LINDA CARR
JOANN SCHMIDT 8

Project Inform, **MARTIN DELANEY** 11

NDA 21-290, Tracleer (bosentan tablets) for
treatment of primary pulmonary hypertension,
Actelion, Ltd.

Sponsor's Presentation:

Overview of Efficacy and Safety: 15
ISAAC KORBIN, M.D.

Drug-induced liver injury: 123
WILLIS MADDREY, M.D., UT Southwestern
Medical Center

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LEWIS RUBIN, M.D., UCSD

Committee Discussion and Review:

Committee Reviewer: **JOANN LINDENFELD, M.D.** 156

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

(8:25 a.m.)

1
2
3 ACTING CHAIR BORER: This is the second day
4 of the 93rd meeting of the Center for Drug Evaluation
5 and Research Advisory Committee. We are going to
6 consider NDA 21-290.

7 Before we begin, JoAnn Standaert, the
8 Executive Secretary of the Committee, will read the
9 Conflict of Interest Statement.

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

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

22 In accordance with 18 USC 208(b)(3), full

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1 waivers have been granted to Doctors Alan Hirsch,
2 Thomas Fleming, Jeffrey Borer, and JoAnn Lindenfeld,
3 which permits them to participate in all official
4 matters concerning Tracleer. A copy of the waiver
5 statements may be obtained by submitting a written
6 request to the Agency's Freedom of Information office,
7 Room 12A30 of the Parklawn Building.

8 In addition, Doctor Hirsch's institution,
9 the University of Minnesota Medical School, is
10 involved in unrelated studies sponsored by United
11 Therapeutics and Glaxo-Smith-Kline. Although these
12 interests do not constitute financial interests in the
13 particular matter within the meaning of 18 USC 208,
14 they could create the appearance of a conflict.
15 However, it has been determined, notwithstanding these
16 interests, that it is in the Agency's best interest to
17 have Doctor Hirsch to participate in the committee's
18 discussions concerning Remodulin.

19 In the event that the discussions involve
20 any other products or firms not already on the agenda,
21 for which an FDA participant has a financial interest,
22 the participants are aware of the need to exclude

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1 themselves from such involvement and their exclusion
2 will be noted for the record.

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

7 That concludes the Conflict of Interest
8 Statement for August 10th.

9 ACTING CHAIR BORER: Thank you.

10 We are going to open the meeting for
11 public comment now. I'll remind anyone who has
12 anything to say that we'd like to know if you have any
13 potentially conflicting financial interests for the
14 record, and whether your travel here was reimbursed by
15 one of the companies involved in this proceeding.

16 With that having been said, I have two
17 people listed who - okay, there are three, who have
18 applied to make comments, and then we'll ask if
19 anybody else does.

20 The first is Linda Carr, who we heard from
21 yesterday.

22 MS. CARR: Good morning.

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1 Members of the committee – can you hear me
2 all right?

3 Good morning – there we go.

4 Members of the committee, thank you again
5 for the opportunity to speak before you and
6 participate in the review process for approval of a
7 new oral drug for the treatment of pulmonary
8 hypertension.

9 Again, I am Linda Carr, President of PHA,
10 and mother of a teenager with PPH who has been treated
11 with Flolan for seven years. For the record, I will
12 submit the full testimony of yesterday as it remains
13 pertinent, but I'd just like to summarize quickly
14 today by simply saying that, as you know PH is a truly
15 devastating disease. It kills adults and it kills
16 children.

17 PHA's position is that, if the science is
18 good, and the medications are safe and effective, we
19 are very anxious for more options, especially oral
20 pill options, for treating pulmonary hypertension.

21 Before closing, I have a short disclosure
22 statement. The Pulmonary Hypertension's mission is to

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1 seek a cure and to provide hope, support and
2 education, and to promote awareness, and to advocate
3 for the pulmonary hypertension community.

4 Consistent with that, and in an effort to
5 fulfill our role in educating the public, the patient
6 population, and physicians treating this disease, PHA
7 has worked with Actelion to create better educational
8 tools through grants provided to PHA. Also with their
9 help, we were able to participate in a satellite media
10 tour yesterday to tell a story that is too often
11 unheard.

12 Once again, I would like to thank the
13 committee for the opportunity to present the views of
14 the Pulmonary Hypertension Association.

15 ACTING CHAIR BORER: Thank you.

16 Does anyone on the committee have any
17 questions for Ms. Carr?

18 Okay, JoAnn Schmidt has asked to speak
19 again today.

20 MS. SCHMIDT: Good morning.

21 Thank you again for giving me the
22 opportunity to address this committee. My name is

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1 JoAnn Schmidt, if you remember me from yesterday, and
2 I have Primary Pulmonary Hypertension.

3 Yesterday, I told you how Remodulin has
4 improved my health and the quality of my life, and
5 today I'd like to talk to you very briefly about
6 Tracleer. Yesterday, I told you how Flolan patients
7 look enviously at those of us on Remodulin, and now
8 it's time for me to confess to you that those of us on
9 Flolan and UT-15 look very longingly at the lucky few
10 people who take oral medication.

11 I'd like to try to explain to you all what
12 it's like to live with a pump, and the best analogy
13 that I can make for you is that it's as if you've
14 grown another arm or leg. Imagine an arm growing out
15 of your stomach, that's what it's like. Having a pump
16 attached to your body changes almost every aspect of
17 your life, how you bathe, how you dress, how you
18 sleep, how you have sex, it affects everything.

19 The other day I tossed the TV remote at my
20 brother, who is on Flolan, and I hit him right where
21 the indwelling catheter enters his body, and I was so
22 scared that I had loosened something and, you know,

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1 you have to react immediately for someone who is on
2 Flolan. But, thankfully, all was well.

3 It really illustrated to me, that fear on
4 his face and his wife's face, that people who wear
5 pumps have to be careful of everything they do, even
6 how they play with their own children. My brother has
7 to be careful about how he interacts with his girls.

8 While family and close friends are
9 familiar with the fact that I wear a pump, there's the
10 outside world to contend with. My pump alarm has gone
11 off at work, try explaining that beeping noise when
12 you are not wearing a beeper, it has gone off on the
13 train, in an elevator, you know, really perfect times.
14 I was asked to dance recently at a wedding, and as my
15 partner put his arm around me he could feel the pump
16 in my side, and these are examples of every-day events
17 that confront people who wear a pump.

18 It's interesting that, you know, when that
19 happens, you know, you have that awkward silence and
20 you know he's felt it, and he doesn't know that you
21 have this illness and you have a stumbling
22 explanation, you see I have this rare lung disease,

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1 you know, blah, blah, blah, it really puts a damper on
2 any kind of social situation.

3 Most PH patients tell their stories and
4 they all have the same theme. The doctor told me I
5 had this horrible disease and I could die, and then
6 they showed me the pump. It is – I can't explain what
7 a double whammy that is, when you realize what the
8 treatment entails. All PH patients dream of the day
9 we will be able to take oral drugs and lose these
10 pumps and the restrictions they come with, and while
11 we are genuinely grateful for drugs like Flolan and
12 Remodulin, we can't help but fantasize of life without
13 them.

14 I hope that Tracleer is approved and we
15 can see our dreams turn into reality.

16 Does anybody have any questions for me?
17 I'll answer anything.

18 ACTING CHAIR BORER: Thank you very much.

19 MS. SCHMIDT: Thank you.

20 ACTING CHAIR BORER: The third request for
21 public comment is from Martin Delaney.

22 MR. DELANEY: I want to thank the committee

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1 for allowing me to speak here today.

2 Some of you, at least the FDA people, I
3 think may already be familiar with me. I've served on
4 any number of FDA advisory committees and task forces,
5 and have taken part in every FDA reform effort for the
6 quickening of the approval of life-threatening
7 illnesses since 1985.

8 The reason I'm here today, first is,
9 obviously, to support the other people speaking with
10 PH for a swift and appropriate approval of this drug
11 should the data warrant it. I haven't seen the data
12 myself, and it's a little awkward to comment on it,
13 obviously, before seeing it, but considering the
14 gravity of the disease and the unsatisfactory nature
15 of the alternative, the existing therapy, I would say
16 this drug, from what I can see, really warrants very
17 careful attention and a swift approval, as long as it
18 has a reasonable balance of safety and efficacy, and
19 I would leave it to the committee's judgment to make
20 that decision.

21 But secondly, and, perhaps, most
22 importantly, I'm here today, in all due respect to the

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1 company and the committee and everyone else, here to
2 demand an immediate expansion of the Compassionate Use
3 Program for Tracleer, because it currently
4 specifically excludes people with HIV. This may just
5 be a carryover from the earlier studies, but at this
6 point this is a profound problem to people like myself
7 working in the AIDS community. It's well known that PH
8 is - that HIV is becoming a significant risk factor
9 for PH, and the existing solution, Flolan, is in many
10 ways counter-indicated for an HIV-infected person, if
11 nothing else because of the greatly increased risk of
12 infection that it poses.

13 So, I don't know what the reason for this
14 is. Whatever it is, I think the people themselves
15 affected by the situation would find it unreasonable,
16 and I urge the companies involved here, both Actelion
17 and Genentech, to make an immediate change in this
18 regard, and I would say this applies also to people
19 with PH category scores higher than two, who are also
20 currently excluded, if I understand the program.

21 I don't use the word "demand" here out of
22 rudeness, but to signal its importance to the

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1 community that I represent. I'm currently in touch
2 with at least a few patients for whom this is a life
3 and death decision, who have looked at the options and
4 are saying, I will not go on Flolan, I will die before
5 I accept that as a choice, and I think that may be a
6 little different from other patient groups because
7 they are facing another underlying life-threatening
8 illness to begin with, and to face that at the same
9 time is then facing a drug which will complicate that
10 problem and add all the other problems of the pump as
11 so beautifully described here just leads some of them
12 to say, I choose not to live under that circumstance.

13 So, I ask this committee to support us in
14 this, and I, as politely as I can, say to the
15 companies, that people with HIV and AIDS have
16 contributed greatly to the ability to move drugs more
17 quickly through the FDA system, everyone has
18 benefitted from their activity, but we are also,
19 perhaps, the group that is most effective at
20 marshaling action, both on a public basis, as well as
21 with the agencies and with the companies, and I'd
22 rather not have to go there as a way of solving this

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1 problem. But, I ask that we solve this problem, and
2 I don't mean three months from now, or two months from
3 now, when approval goes through, I'm talking about
4 people who need this change made in the next five to
5 ten days or they will choose not to live, rather than
6 go forward with the options left for them.

7 Thank you for your attention.

8 ACTING CHAIR BORER: Thank you.

9 Does anyone on the committee have any
10 questions for Mr. Delaney?

11 Thank you very much.

12 Is there any other comment from a member
13 of the public? If not, we'll go forward with the
14 sponsor's presentation, to be introduced by Doctor
15 Korbin.

16 DOCTOR KORBIN: Doctor Borer, Doctor
17 Lipicky, Doctor Temple, members of the committee,
18 today we are going to present to you data that would
19 show that bosentan is an effective treatment for
20 Pulmonary Arterial Hypertension. Its treatment,
21 however, is also associated with risks that are
22 directly related to the increased incidence of

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1 elevated liver aminotransferases and to a lesser
2 extent to the decrease in - concentration.

3 Nevertheless, we'll try to show you that
4 the benefit of the drug outweighs its risks,
5 especially in the context of a life-threatening
6 disease with a poor quality of life like Pulmonary
7 Arterial Hypertension for which there are very limited
8 treatment options.

9 Today, we have with us several advisors
10 who are experts in their fields, and they will be glad
11 to answer your questions. Doctor Rubin, for Pulmonary
12 Arterial Hypertension, Doctor McLlain for Preclinical
13 Toxicology, Doctor Rowland for Clinical Pharmacology,
14 Doctor Maddrey for Hematology, and Doctor Spevak for
15 Hematology.

16 In our presentation today, we will cover
17 shortly the rationale for a - receptor antagonism in
18 this disease, preclinical observations and clinical
19 pharmacology. Then we will go into more details into
20 the efficacy of the drug in patients with Pulmonary
21 Hypertension, overall safety - and then the specific
22 issues, the specific safety issues associated with the

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1 drug.

2 Doctor Maddrey will cover shortly the
3 topic of drug-induced liver injury, and Doctor Rubin
4 will summarize the risk benefits associated with the
5 drug.

6 Endothelium belongs to a family of 21
7 aminoacid peptides. It is synthesized and secreted by
8 the endothelial cells. It acts with two receptors,
9 endothelium A and endothelium B. Through these two
10 receptors, it induces vasoconstriction, fibrosis,
11 hypertrophy and hyperplasia. And, it also increases
12 vascular vulnerability.

13 What is the rationale for using
14 endothelium receptor antagonistic, it's shown that in
15 patients with Pulmonary Arterial Hypertension there is
16 an increase in plasma endothelium 1 levels, and these
17 levels correlate with the disease's severity. It was
18 also shown that there is an increase in endothelium 1
19 immunoreactivity in the lung vasculature, in the
20 specific plexiform lesions. Therefore, it is expected
21 that the blockade of endothelium 1 activity and -
22 effect might be effective in patients with Pulmonary

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1 Arterial Hypertension. And, indeed, it was shown in
2 preclinical models that this might be the case.

3 Bosentan is a specific low molecular
4 weight competitive endothelium receptor antagonist.
5 It inhibits the effect of endothelium 1 by inhibiting
6 both receptors, endothelium A and endothelium B. It
7 was tested in several - models. Pulmonary
8 hypertension induced by chronic hypoxia or
9 monocrotaline, pulmonary fibrosis induced by -mycin,
10 pulmonary inflammation induced by cephadex and -

11 In all these studies, what was found out
12 that the main effects of bosentan were a decrease in
13 pulmonary - pressure, a decrease in pulmonary vascular
14 hypertrophy and - trophy and a decrease in pulmonary
15 fibrosis and inflammation, all of which indicate that
16 it might be effective in patients with Pulmonary
17 Arterial Hypertension.

18 Additional preclinical observations were
19 found to be related to human safety, teratogenicity,
20 decrease in red blood cell parameters in liver injury,
21 which we will touch in detail during the safety
22 presentation.

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1 One last topic on preclinical that I
2 would like to touch is related to a question that was
3 given to you during your deliberation, and this is
4 related to observations of testicular changes in
5 preclinical studies or toxicology studies. And,
6 indeed, in a two-year rat study increased incidence of
7 slight testicular tubular atrophy was observed. It
8 was not observed in a two-year mouse study.

9 Looking at all the preclinical and
10 toxicology studies, it looks that the overall pattern
11 and findings were not typical of drug-induced
12 testicular toxicity, and also there was no effect on
13 sperm count, fertility, or male fertility in a six-
14 week rat study in which bosentan was given at doses 50
15 times above the recommended human doses.

16 Doctor McLlain, who is with us today, will
17 be glad to expand on this issue during your
18 deliberation, if you will be interested to hear more
19 about this issue in relation to bosentan and maybe
20 beyond bosentan.

21 Twenty-three studies were performed in
22 clinical pharmacology. The objective of these studies

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1 was to characterize the pharmacokinetic properties of
2 the drug, to look for potential drug/drug interaction,
3 and proof of concept studies. Let me summarize the
4 main observations.

5 The pharmacokinetic characteristics were
6 found to be dose proportional up to 600 mg single dose
7 or 500 mg per day as multiple dose. The maximum
8 concentration is achieved within 3.5 hours. There is
9 no relevant - effect, and the oral bioavailability is
10 approximately 50 percent.

11 Bosentan, its terminal half life is 5.4
12 hours. It is bound to protein 98 percent, mainly to
13 Albumin. It's steady state is reached within three to
14 five days. Age, gender, race, body weight and renal
15 function appeared not to have a relevant effect on
16 pharmacokinetic properties.

17 Bosentan is eliminated mainly by hepatic
18 metabolism and subsequent biliary excretion. Its main
19 metabolic pathways are sip 3A4 and sip 2C9, and it is
20 expected, therefore, if one blocks these enzymes that
21 the concentration of bosentan might increase. And,
22 indeed, when it was given with ketoconazole, which is

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1 a strong inhibitor of – 3A4 there was only a modest
2 increase in bosentan concentration, only two fold. In
3 fact, 3A4 is more important than 2C9 enzyme
4 metabolism, therefore, it is expected that inhibition
5 of 2C9 is not going to exert a greater effect than
6 Ketoconazole. Cyclosporin A, a non-specific inhibitor
7 of transporters, markedly increased bosentan exposure.

8 Bosentan does not inhibit sip 1A2, 2C9,
9 2C19, 2 – and 3A4. Therefore, it is not expected that
10 the plasma concentration of other drugs will increase
11 when given concomitantly with bosentan.

12 Bosentan, however, induces 2C9, 2C19 and
13 3A4. And, indeed, in healthy volunteer studies it was
14 found out that there was a decrease in exposure of
15 substrates of 2C9 and 3A4 by a modest level of therapy
16 to 60 percent.

17 Therefore, it is expected that the reduced
18 efficacy might be observed for 2C9 and 3A4 substrates.
19 We wanted to look into the clinical relevance of this,
20 if, indeed, this is translated into clinical
21 relevance, and one of the drugs that is going to be
22 given concomitantly in high frequency of patients is

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1 Warfarin, and in the hospital and field studies it was
2 found out that there was a 30 percent reduction in the
3 exposure to Warfarin when it's given with bosentan.

4 And, indeed, in our large Pulmonary
5 Arterial Hypertension study quite a number of patients
6 took both bosentan, 34 patients on the placebo, and 59
7 on bosentan, two concomitantly Warfarin. And, we
8 looked at different aspects and we found out that
9 there was no change in Warfarin dose when we compared
10 baseline to end of treatment, no change in INR when we
11 compared baseline to end of treatment, and there was
12 no difference in Warfarin dose change as a result of
13 changes in INR or adverse events when we compared
14 bosentan to placebo, so overall the 30 percent
15 reduction in Warfarin exposure did not translate to
16 any clinically relevant observation when it comes to
17 Warfarin.

18 Let me move now to the efficacy results
19 with bosentan. The efficacy results are based mainly
20 on two studies, which we addressed the studies 351 and
21 352, in 245 patients. In both studies, patients were
22 offered to go into an open label extension study, 353

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1 after 351, and 354 after 352, and we can see that most
2 patients, indeed, entered the open label studies, 29
3 of the 32 patients, and 200 out of the 213 patients.

4 What was the design of these two studies?
5 It was very much the same. After screening, patients
6 were randomized to receive either placebo or 62.5 mg
7 twice a day in both studies for four weeks. After
8 four weeks, in the 351 study the dose was increased to
9 125 mg twice a day for additional eight weeks until
10 the end of period one. In the second, the largest,
11 study, the dose was increased to either 125 mg twice
12 a day or to 250 mg twice a day for an additional 12
13 weeks up to week 16. In both studies, patients
14 continued double blind treatment beyond the primary
15 evaluation of period one, and they went into period
16 two. It was variable in the first study and fixed in
17 the second study.

18 Let me explain this, because this is an
19 interesting difference between the trials. Let me
20 start with the smaller study, 351. In this study,
21 this is the randomization of patients from the first
22 patient to the 32nd patient. Now, the study - every

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1 patient that completed the 12 weeks of treatment
2 continued also in the double blind treatment into
3 period two, until the last patient that was randomized
4 completed 12 weeks of treatment, so this was variable
5 and every patient was in this period during a
6 different period of time.

7 This was different in the larger study,
8 where again this is the recruitment from the first
9 patient to the last patients, however, it was decided
10 that all the patients that were randomized during this
11 period will be assigned to complete period two after
12 28 weeks. So, up front they were assigned the first
13 48 patients, in fact, it had been were assigned to
14 complete 28 weeks of double blind treatment.

15 What were the main inclusion criteria?
16 Males or females, age 12 years or older, Pulmonary
17 Arterial Hypertension due to primary pulmonary
18 hypertension or secondary to Scleroderma or other
19 connective tissue diseases, WHO functional class 3 or
20 4. The baseline six minute walk, this had to be
21 between 150 to 450 meters in the large study or 500
22 meters in the smaller study, and, of course, they had

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1 to have evidence for Pulmonary Arterial Hypertension,
2 and, indeed, the Pulmonary Arterial Hypertension had
3 to be above 25 millimeter mercury, pulmonary - score
4 resistance above 40 and weight pressure below 15.

5 The main exclusion criteria, other reasons
6 for Pulmonary Arterial Hypertension. If patients with
7 scleroderma and Pulmonary Arterial Hypertension had
8 severe interstitial fibrosis, systolic blood pressure
9 less than 85 millimeter mercury, if the baseline liver
10 aminotransferases were more than three times the upper
11 limit of normal, or if the hemoglobin or hematocrit
12 was more than 30 percent below the lower limit of
13 normal. If the treatment for Pulmonary Arterial
14 Hypertension was changed in the last month before
15 screening, patients were not allowed, of course, this
16 does not include anticoagulants, and if they received
17 epoprostenol in the last few months before screening
18 they were not allowed to go into the trial.

19 So, what patients entered the trials?
20 And, I'll show you the results on the left side, study
21 351, and on the right side study 352. You can see
22 that, indeed, most patients were women in both

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1 studies, the age between 47 to 52, the weight slightly
2 higher in the smaller study compared to the larger
3 study, 80 to 90 percent of the patients were White,
4 but 80 percent of the patients were studied in the
5 U.S. in the smaller study and 55 percent in the larger
6 study.

7 In the smaller study, all patients were
8 WHO functional class 3, but in the larger study 6 and
9 10 percent of the patients were class 4. The time
10 from diagnosis was about 2.5 years, and most patients
11 had primary Pulmonary Arterial Hypertension, but we
12 also had quite a substantial number of patients with
13 scleroderma, and also other diseases. The other
14 diseases were mainly mixed connective tissue disease
15 or lupus erythromotosis.

16 The baseline hemodynamics were typical of
17 patients with Pulmonary Arterial Hypertension,
18 pulmonary arterial pressure of more than 50 millimeter
19 mercury, pulmonary vascular resistance more than 800,
20 cardiac index on the low side, weight pressure normal,
21 and right arterial pressure slightly elevated.

22 Concomitant indications, we can see that

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1 anti-thrombotics, 70 to 80 percent of the patients.
2 Diuretics, interestingly, in the smaller study almost
3 90 percent of the patients took diuretics compared to
4 50 percent in the larger study. Calcium antagonists,
5 50 percent of the patients. Cardiac glycosides 10 to
6 20 percent of the patients, and oxygen was used
7 between 10 to 30 percent of the patients.

8 What about the patient disposition? In
9 the smaller study, the 32 patients that were
10 randomized 11 took placebo and 21 took bosentan 125 mg
11 twice a day. We can see that in the placebo group
12 three patients were withdrawn, all of them because of
13 worsening Pulmonary Arterial Hypertension and none in
14 the bosentan group, and, of course, this consisted
15 both in the intent-to-treat and the safety population.
16 We can see that all the ex-bosentan patients entered
17 the open label trial, and eight of the 11 patients of
18 the placebo entered the open label trial.

19 In the larger study, 214 patients were
20 randomized to either placebo, 125 mg twice a day
21 bosentan, or 250 mg twice a day bosentan. One patient
22 that was randomized never got treatment, this was a

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1 patient in Australia that was living about 1,000 miles
2 away from the center, and he was told not to start
3 treatment before the center speaks with the sponsor,
4 and once they spoke with the sponsor we found out that
5 he did meet the entry criteria, he had congenital
6 heart disease, so he was told not to start any
7 treatment.

8 We can see the disposition of the
9 patients. Six patients were withdrawn from the
10 placebo group, three from the 125 mg, and three from
11 the 250 mg, and we can see that almost all the
12 patients that completed period one also entered the
13 open label trial, all the bosentan patients and 62 of
14 the 63 patients from the placebo.

15 What were the efficacy parameters? The
16 primary parameter in both studies, the six minute walk
17 test at the end of period one. Secondary parameter,
18 time to clinical worsening, which was a composite of
19 death, hospitalization due to Pulmonary Arterial
20 Hypertension, discontinuation due to worsening
21 Pulmonary Arterial Hypertension, start of epoprostenol
22 or lung transplantation or septostomy, none of the

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1 patients had this complication.

2 Other secondary parameters, change
3 involved with Borg indexes, change in WHO functional
4 class, change in pulmonary hemodynamics, this was
5 evaluated only in study 351, and we evaluated the need
6 for an increasing therapy for Pulmonary Arterial
7 Hypertension during period one in the larger study.

8 What were the statistical approaches for
9 the primary parameter? In study 351, it was the
10 student's t-test, in study 352 the Mann-Whitney U-
11 test.

12 How did we manage patients with no valid
13 assessment at the end of period one? If it was due to
14 Pulmonary Arterial Hypertension, or because of death,
15 they got a zero meter, and this happened in one
16 placebo patient in the smaller study and in the larger
17 study it was in three placebo patients and two
18 bosentan patients on 125 mg twice a day. If the
19 reason was different from these reasons, then the last
20 value was carried forward.

21 What were the results of the two studies?
22 You can see on the next slide that the mean and the 95

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1 percent confidence limits, you can see that in the
2 smaller study on the upper part there was a treatment
3 effect of about 76 meters and we the confidence limit
4 and the p-value. In the second study, the treatment
5 effect was 44.2 meters, with a p-value of 0.0002.
6 Also, each dose versus placebo was significant,
7 remember that this was the primary parameter and this
8 was an exploratory approach to each dose versus
9 placebo, they were also significantly better than
10 placebo, but the 250 mg seemed to be slightly better
11 than the 125, although the difference was not
12 significant.

13 We looked at the data from different
14 aspects to see the robustness of results, and let me
15 show you some of what we have done. As you have seen,
16 the Mann Whitney u-test was the primary evaluation in
17 the 352 study, so we applied it also for 351. Also,
18 we looked at the per-protocol population which was
19 significant for both trials.

20 In the larger trial, we had more patients
21 than expected, so we looked at it based on the sample
22 size planned for the trial, which was 100 – the first

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1 150 patients, and this was the effect. Then we said,
2 okay, let's use differently the replacement tools. If
3 we do carry forward for all the patients, without
4 giving the worst criteria, these were the p-values.
5 If we give zero substitution to all the patients at
6 the end of period one assessment, this was the p-
7 value. If we give the - take the placebo patients,
8 give them carry forward and all bosentan patients
9 zero, this is what we get. And, if we exclude the
10 patients on placebo who didn't finish the trial and
11 give zero to bosentan patients, this is what we get.
12 You don't see the numbers here, because if we do these
13 it always becomes better for bosentan.

14 What was the time course in these two
15 trials? The upper part we see the smaller trial, 351,
16 and here is 352. Already at week four in both trials
17 there was an apparent increase in walk test with the
18 62.5 mg in both studies. There was also a placebo
19 response at week four, but this appeared over time
20 they could not maintain it, while in the bosentan
21 group there was -, they increased the dose to 125 mg
22 twice a day, or 250 mg twice a day, and we see a

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1 further increase at week eight, which was maintained
2 up to week 12, in this study out to week 16, in this
3 study, in effect, the patients who completed week 28,
4 and I'll show you this later on, also maintained these
5 effects on double blind treatment up to week 28.

6 When we looked at each dose versus placebo
7 in the larger study, it seems that the higher dose is
8 slightly better than the lower dose, but interestingly
9 this difference was already apparent at week four when
10 both arms were treated with the 62.5 mg of the drug.

11 We looked in the larger study at different
12 sub-populations to see if there is any sub-population
13 who is not responding to the drug, and we looked at
14 different angles. This is the overall effect of the
15 trial, and we can see the mean and the 95 percent
16 confidence intervals based on gender, different age
17 groups, weight, race, WHO functional class 304,
18 etiology, primary Pulmonary Hypertension or
19 scleroderma with Pulmonary Hypertension, time from
20 diagnosis, history of congenital heart disease,
21 location, U.S. versus non-U.S., baseline hemodynamics,
22 and baseline walk test, and it was always consistent

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1 with the positive treatment effect for all the sub-
2 groups we evaluated.

3 The increase in walk test, the patients
4 not only improved the walk test, but also were able to
5 do this with a decrease in the Borg Dyspnea Index and
6 again we see here the mean and the 95 percent
7 confidence intervals for the smaller study and for the
8 larger study in these two studies.

9 The other secondary parameter was the time
10 to clinical worsening, and let me remind you that this
11 was either death, worsening heart failure, resulting
12 in hospitalization or discontinuation, or start of
13 epoprostenol.

14 This is the smaller study, and as you'll
15 remember three patients deteriorated in the smaller
16 study because of Pulmonary Arterial Hypertension has
17 already reached the significant level, but I think
18 that it is much more impressive in the larger study,
19 and we can see that the patients on placebo are
20 deteriorating fast compared to bosentan patients,
21 already at the end of period one it was significantly
22 different, and the numbers that you see here are the

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1 patients at risk for this evaluation.

2 When we looked at each dose versus placebo
3 in the larger study, there was no difference between
4 the doses and placebo, we saw the same effect.

5 Now, if you look at the different
6 components of the time to clinical worsening, what we
7 saw was that there was no one component that was not
8 more frequent among bosentan patients, in favor or
9 bosentan patients. You can see that in the smaller
10 study these are the three patients that deteriorated,
11 in the large study 20 percent of the patients
12 deteriorated on placebo compared to 6 percent of the
13 patients, it was mainly coming from many more
14 hospitalizations among the placebo patients for
15 Pulmonary Arterial Hypertension, but we can see that
16 each component was better on bosentan compared to
17 placebo.

18 Then we looked at the WHO functional
19 class, and we looked at it in two different ways. How
20 many patients improved? And, we can see in the
21 smaller study 9 versus 43 percent, in the larger study
22 30 versus 42 percent. In fact, if you combined the

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1 evaluation of these two studies and you see below the
2 treatment difference was 14.9 percent, and these are
3 the confidence limits.

4 When we looked at the whole distribution
5 of the WHO functional class, how many worsened by one
6 class, no change, improved by one class or improved by
7 two classes, and we can see that more patients on
8 placebo in both trials deteriorated, and more patients
9 improved in both studies by one class, and a few
10 patients even by two classes. And, in both studies
11 this was statistically significant.

12 The hemodynamic parameters went in the
13 same direction as the clinical endpoints. You can see
14 that pulmonary vascular resistance, pulmonary artery
15 pressure, weight pressure, right arterial pressure,
16 and especially cardiac index all improved
17 significantly. We can see the mean and the 95 percent
18 confidence intervals for all these hemodynamic
19 parameters.

20 Another aspect that we looked to see if it
21 also goes in the same direction was the need for
22 additional therapy for Pulmonary Arterial

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1 Hypertension. This does not include anti-thrombotic,
2 it was mainly treatment for heart failure, and what we
3 can see, that there was a tendency among the placebo
4 patients to increase at least once the treatment
5 compared to bosentan, and the same thing to increase
6 the treatment at least twice during treatment, about
7 19 percent on placebo and 11 percent on bosentan.

8 Let me show you what we have seen at week
9 28 of the double blind treatment, and let me just
10 remind you that in the small study it was variable so
11 it's very difficult to assess the effect on this
12 trial, but still I'm going to show you the data, and
13 as you'll remember eight in 21 patients entered and
14 completed period two.

15 In the larger study, remember that 48
16 patients, from the beginning, were assigned to go up
17 to week 28 for double blind treatment, and the
18 assignment of these 48 patients to the three treatment
19 groups, and we see here what was the patient
20 disposition until they finished period two, and all
21 those that were assigned to period one also were
22 assigned to period two.

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1 And, this is what we have seen. This is
2 the smaller study, and here we put it in cohorts, so
3 only patients who finished week 28 are looked all over
4 from the start, or patients who finished week 20, this
5 is their cohort. But, this is again, this is a
6 variable period, hard to estimate it, although it
7 looks like it goes in the right direction.

8 In study 352, we see the effect in the
9 placebo patients that were assigned to 28 weeks, and
10 the bosentan patients that were assigned to 28 weeks,
11 and we clearly see that the effect is maintained up to
12 28 weeks of double blind treatment.

13 The long-term effect is also coming from
14 the open label extension study 353. In this trial,
15 when patients finished the small study the placebo
16 patients started on 62.5 mg twice a day, and the 125
17 mg twice a day patients of bosentan went down to 62.5
18 mg twice a day for four weeks, before going to the
19 higher dose.

20 During these trials, there was an
21 amendment of the possibility of increasing to 250 mg
22 twice a day, in order to make it similar to study 354,

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1 and we can see, as mentioned before, eight of the 11
2 placebo patients went into this trial, and all the ex-
3 bosentan.

4 Walk test was evaluated at week four, and
5 the WHO functional class every six months, and this is
6 what we have seen. The ex-placebo - the ex-bosentan
7 patients maintained their gain during the 351 trial,
8 with maybe a minor increases failure of the walk test.
9 What is interesting, and this is with a slight
10 decrease in the dose to 125 to 62.5, the ex-placebo
11 patients increased their walk test by 22.5 meters, and
12 what is important is that for most patients this
13 evaluation was done when the investigators and the
14 patients did not know the treatment code of the
15 patients in study 351.

16 WHO functional class, all the patients
17 were class 3 at the start of 351 trial, and we can see
18 that about half after six months in the open label
19 were in class 3, 12 in class 2 and one in class 1.
20 One patient deteriorated and had to be put on
21 epoprostenol, and this was maintained also after one
22 year of treatment.

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1 So, let me summarize the efficacy of the
2 evaluations. Bosentan 125 and 250 mg twice a day
3 versus placebo, increased exercise capacity, it was
4 consistent in all sub-populations, there was an
5 improvement in dyspnea on exercise, and improvement in
6 WHO functional class, all of which suggests that
7 patients might be able to improve their daily life
8 activities.

9 There was an improvement in pulmonary
10 hemodynamics, and there was a decrease in the risk of
11 clinical worsening, suggesting that maybe bosentan can
12 affect the clinical course of the disease. With
13 extended treatment, we have seen that the clinical
14 benefits are maintained with no evidence for
15 tolerance.

16 I wonder if you would like to break for
17 questions.

18 ACTING CHAIR BORER: Does anyone have any
19 specific questions for Doctor Korbin?

20 JoAnn?

21 DOCTOR LINDENFELD: That was a very nice
22 presentation and a nice set of studies.

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1 I want to go back to the pharmacokinetics
2 because I think this is the correct time to do that,
3 and then go on to the efficacy.

4 I didn't hear a description of the
5 pharmacokinetics of oral bosentan in Pulmonary
6 Hypertension patients, that is with oral bosentan.
7 Could you tell us something about that?

8 DOCTOR KORBIN: We did not study the
9 pharmacokinetics in patients with Pulmonary Arterial
10 Hypertension. We did have studies in patients with
11 CHF, and our assumption was that these patients are
12 having more or less the same kind of
13 pathophysiological situations regarding the - both the
14 Pulmonary Hypertension and the right heart failure.
15 And, indeed, in patients with severe congestive heart
16 failure there was about a 30 percent increase in the
17 concentrations or the exposure to bosentan in these
18 patients, and we believe that this is what we might
19 see also in patients with Pulmonary Arterial
20 Hypertension.

21 DOCTOR LINDENFELD: So, there is no data on
22 oral pharmacokinetics in this disease.

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1 DOCTOR KORBIN: We did not study in our
2 program the pharmacokinetics in these patients.

3 DOCTOR LINDENFELD: And, you would guess
4 also that there's a very big difference in the types
5 of drugs that those two classes of patients are on.
6 In other words, I would expect heart failure patients
7 to have a much larger number of drugs with more
8 potential interactions than the Pulmonary Hypertension
9 group of patients.

10 DOCTOR KORBIN: That's so. In fact,
11 patients with congestive heart failure took many more
12 drugs than patients with Pulmonary Arterial
13 Hypertension, where you expect maybe even to see more
14 interaction if there might be an interaction.

15 DOCTOR LINDENFELD: And, the average age of
16 heart failure patients versus pulmonary hypertensions,
17 I would guess, would be different?

18 DOCTOR KORBIN: Slightly higher.

19 DOCTOR LINDENFELD: Substantially different
20 gender differences in those two populations?

21 DOCTOR KORBIN: In pulmonary arterial
22 hypertension it was mainly women, and, of course, in

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1 CHF it was about 30 to 40 percent women.

2 DOCTOR LINDENFELD: Okay.

3 And, tell me something about the
4 pharmacokinetics in children. We've heard something
5 about children here. Tell me what you know about the
6 pharmacokinetics in children.

7 DOCTOR KORBIN: We have a study going on
8 now in children, and we do have data that we did not
9 submit yet to the Agency, where we see that the
10 pharmacokinetics are, in fact, the same as in CHF
11 patients, about 40 percent increase in plasma
12 concentration.

13 I wonder if our pharmacokineticist could
14 comment on the observations in the children on
15 pharmacokinetics.

16 DR. MONSUR: Yes. Doctor Korbin is correct
17 when stating that the exposure to bosentan in
18 patients, a very limited number of pediatric patients
19 so far tested to this drug, is about 30 to 40 percent
20 higher than seen in healthy subjects. We have a slide
21 on that, No. 32.

22 DOCTOR LINDENFELD: Okay, and in children

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1 can you give me some idea of an age range? Is there
2 a difference in an eight year old than a 14 year old?

3 DR. MONSUR: Yes, this is just the start of
4 the study, and in single doses the body weight range
5 is 20 to 40 kilogram here.

6 DOCTOR LINDENFELD: Okay.

7 Let me then just go on, body weight, there
8 was no correction in dose in this study for body
9 weight, but I assume there's a fairly large difference
10 in concentrations by body weight?

11 DOCTOR KORBIN: In study 352, it was
12 recommended that patients with body weight less than
13 40 will get half the dose. In fact, the condition was
14 that they would not go beyond 62.5 mg twice a day, and
15 it occurred only in a couple of patients.

16 DOCTOR LINDENFELD: Okay.

17 And then, I want to move on to some of the
18 drug interactions. We've seen that Ketoconazole and
19 Cyclosporin are contraindicated because of the large
20 increase in bosentan levels.

21 DOCTOR KORBIN: Not Ketoconazole, only
22 Cyclosporin.

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1 DOCTOR LINDENFELD: Well, I think
2 Ketoconazole, at least in the FDA briefing packet, was
3 suggested that it should be contraindicated.

4 DOCTOR KORBIN: We believe that it is
5 appropriate to contradict for Cyclosporin but not for
6 Ketoconazole because the increase in plasma
7 concentration is only twofold.

8 DOCTOR LINDENFELD: That's in the steady
9 state, but bosentan goes up 30-fold acutely.

10 DOCTOR KORBIN: No, no, only for
11 Cyclosporin, this was - levels on day one, it has
12 nothing to do with 3A4, it is related to the other
13 transponder mechanism, and we checked it in
14 Ketoconazole and there was only twofold increase, and
15 it is completely different from Cyclosporin.

16 DOCTOR LINDENFELD: Okay.

17 Now, what can you tell me about Intestinal
18 3A4, is there any interaction, for instance, with
19 grapefruit juice? Do we see a marked increase?

20 DOCTOR KORBIN: Again, I would like to ask
21 our pharmacokineticist to answer this.

22 DR. MONSUR: Yes, once again. Ketoconazole

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1 is a very potent inhibitor of 3A4, and it inhibits 3A4
2 both in the gastro and intestinal tract and in the
3 liver. With bosentan, however, we are dealing with a
4 low clearness drug, so the first pass effect is
5 virtually not existent, so only the 3A4 content
6 activity in the liver is of importance when dealing
7 with bosentan.

8 DOCTOR LINDENFELD: Okay.

9 And then, let me go on for a minute, this
10 is a highly protein-bound drug, and I know you
11 discussed that a bit with Digoxin and Gloglencolone,
12 but I'm concerned there's a lot of highly protein-
13 bound drugs here. Do we have any in vivo data? I know
14 there's a little bit of in vitro data, but do you have
15 any in vivo data about the effect of protein binding?

16 DOCTOR KORBIN: Again, I would like our
17 pharmacokineticist to answer this.

18 DR. MONSIEUR: We have tested the protein
19 binding, potential protein binding displacement
20 interactions with bosentan for a number of drugs.
21 This has to be done in vitro. However, we looked
22 specifically at the drugs which had shown an

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1 interaction in vivo.

2 For instance, Warfarin, a very clinically
3 relevant drug, and also Gliboride, and there was no
4 indication whatsoever that there is an interaction at
5 the protein binding level between these drugs and
6 bosentan.

7 DOCTOR LINDENFELD: Then help me
8 understand, because I think in the briefing book it
9 says that, for instance, the levels of Phentoin go up
10 30 percent, is that not correct, did I miss that in
11 the briefing book? Digitoxin 20 percent, I believe
12 there's a - I'll have to go back and find the page
13 number, but I think that's -

14 DR. MONSUR: It's correct that the in vitro
15 binding data show a slight increase in the free
16 fraction of bosentan by Phentoin and Digitoxin, but
17 a 20 percent change in the free concentration of
18 bosentan is likely to be of no clinical important..

19 DOCTOR LINDENFELD: Well, and then the same
20 data suggests 80 percent for Tolbutamide increase in
21 bosentan levels.

22 DR. MONSUR: That's correct.

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1 DOCTOR LINDENFELD: Okay.

2 And, what can you tell me about other
3 highly protein bound drugs, for instance, Valium?

4 DR. MONSUR: Valium has not been tested,
5 but it's unlikely that there will be an interaction at
6 this level.

7 DOCTOR LINDENFELD: Ceftriaxone? I have a
8 whole list of highly protein bound drugs bound to
9 Albumin. I just wonder how much - I'm just concerned
10 about -

11 DOCTOR KORBIN: Maybe we can ask Professor
12 Rowland to answer this question, because he has a lot
13 of experience in this issue.

14 DOCTOR ROWLAND: Malcolm Rowland. I can
15 talk about protein binding, there are many drugs which
16 are highly protein bound, and the issue that we've
17 discussed is the effect of the other drugs on
18 bosentan. Bosentan itself, of course, its
19 concentrations are too low to displace other drugs.

20 The other drugs that you mentioned, like
21 Valium and so forth, also at concentrations are not
22 capable of occupying enough of the binding site to be

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1 significant displacers. And, the only one that you
2 did refer to, which was Tolbutamide, you have to get
3 up to concentrations around greater than 100 mg/l, and
4 I think in the actual study that was done they did a
5 250 mg/l in vitro to really see any significant
6 changes in the actual fraction bound of bosentan.

7 DOCTOR LINDENFELD: Okay.

8 DOCTOR ROWLAND: And, these are very rare
9 events, I mean, to get up to those concentrations of
10 a drug bound to Albumin is very uncommon.

11 DOCTOR LINDENFELD: And then, let me just
12 - that's helpful information, but let me ask you
13 about, since most of these patients, many are on
14 Warfarin, what about combinations of some of these
15 drugs which many of them are very common, so what
16 about patients that are on two or three of these
17 drugs, will there need to be instructions to
18 physicians about how to use those?

19 DOCTOR ROWLAND: No, not in terms or
20 protein binding, because in all of those ones,
21 including Warfarin, the concentrations of Warfarin are
22 so low relative to the binding capacity of Albumin.

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1 Albumin, as you know, is the most abundant plasma
2 protein that exists.

3 DOCTOR LINDENFELD: Right.

4 I'm not just concerned about Warfarin
5 alone, but what about combinations of two or three of
6 these drugs that are highly protein bound?

7 DOCTOR ROWLAND: Even so, I think the sum
8 of those concentrations are not going to get anywhere
9 near the actual capacity of the Albumin.

10 DOCTOR LINDENFELD: Okay.

11 And, the in vivo data for that?

12 DOCTOR ROWLAND: Well, I think there's been
13 a lot of studies done over the years with regard to
14 many of these highly protein bound drugs, and their
15 propensity to (A) displace, and to show clinical
16 significance. The number of times clinically it has
17 been shown that the fraction on bound substantially
18 increases is very few, and in none of those cases has
19 there been a clinically significant interaction shown
20 associated with displacement, and that has been
21 observed over many years.

22 DOCTOR LINDENFELD: Okay.

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1 And, what level, given this excess
2 capacity of Albumin, at what level would the Albumin
3 have to fall to make this a problem?

4 DOCTOR ROWLAND: Oh, you've got - in the
5 case of normal Albumin, you've got to get up to - of
6 average concentrations of drugs, you've got to get in
7 the order of 50 mg/l and higher before you see
8 anything. If you get into very low Albumin states,
9 nephritic syndrome or the like, those sort of
10 conditions, then you can go down to about 20/30 mg/l
11 before you start to see it.

12 DOCTOR LINDENFELD: Okay.

13 And, we might ask, how many patients with
14 primary pulmonary hypertension have fairly low Albumin
15 levels? I know it's a percentage, I just don't know
16 how high it is.

17 DOCTOR KORBIN: I don't know the
18 percentage, but almost none had low Albumin.

19 DOCTOR LINDENFELD: Okay.

20 I just want to ask about enzyme induction.
21 We have data that this occurs, and I saw data up to
22 day 11, does it occur beyond day 11? Do we see

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1 additional enzyme induction?

2 DOCTOR KORBIN: The steady state is reached
3 after three to five days. In fact, bosentan is
4 inducing its own metabolism and the concentration goes
5 down after three to five days. If we have data, if
6 you'd like we can show you, that after three to five
7 days, in fact, after seven days there is nothing
8 happening anymore.

9 DOCTOR LINDENFELD: Okay.

10 Maybe if anybody wants to ask any other
11 pharmacokinetic questions?

12 ACTING CHAIR BORER: We have Steve, and I
13 think I saw Alan after that.

14 DOCTOR NISSEN: I didn't have a
15 pharmacokinetic question, but I was very struck by the
16 hemodynamic data. If I'm correct, it went by kind of
17 quickly, but the baseline PVRs were in the sort of
18 800/900 range, and you were seeing a change of about
19 400. So, is it correct that pulmonary vascular
20 resistance was reduced by about 50 percent in those
21 patients that you studied, is that correct?

22 DOCTOR KORBIN: That's correct.

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1 DOCTOR NISSEN: Yeah.

2 DOCTOR KORBIN: And, maybe we can see the
3 hemodynamic slide again, this will help us in looking
4 at it. This is slide 45.

5 DOCTOR ARMSTRONG: Just on that point,
6 Steve, I was impressed that most of that was driven by
7 the change in cardiac output. There was very little
8 change in pulmonary pressure.

9 DOCTOR KORBIN: In this there was a large
10 increase in cardiac output, and there was also a
11 decrease in pulmonary artery pressure, but you are
12 right, there was a striking decrease in pulmonary
13 vascular resistance.

14 I think that Doctor Rubin might want to
15 comment on this, because he treated many of these
16 patients and he has seen this data in these patients.

17 ACTING CHAIR BORER: Before you make any
18 comment, can you just clarify for us when these
19 measurements were made? My recollection from your
20 presentation book is that they were made after the
21 six-minute walk test at the end of period one, if I'm
22 not mistaken.

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1 DOCTOR KORBIN: That's correct, in order
2 not to -

3 ACTING CHAIR BORER: How soon after the
4 six-minute walk test, was the catheter in at the time
5 the six-minute walk test was done, or how soon
6 afterwards were they done?

7 DOCTOR RUBIN: Usually within an hour or
8 two, depending on availability.

9 ACTING CHAIR BORER: Okay.

10 DOCTOR RUBIN: But, the catheter - the walk
11 test was done without a catheter in.

12 DOCTOR LINDENFELD: This hemodynamic data
13 is from 351?

14 DOCTOR KORBIN: This is the smaller study,
15 we didn't do hemodynamics in the larger study.

16 DOCTOR LINDENFELD: In which there were 30
17 patients, and all the benefits were substantially
18 greater in that study.

19 DOCTOR NISSEN: Sure. I recognize that
20 it's a very small number of people studied, but it
21 just, to me, is a very, very large effect, and I
22 wanted to explore it a little bit more. But, please,

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1 comment, if you would, first, and then -

2 DOCTOR RUBIN: I'm happy to answer any
3 question. I would say that the changes are both
4 pressure and output, clearly output greater than
5 pressure. Just to put it in perspective, the changes
6 are not too dissimilar from those seen with
7 epoprostenol, and even small changes in pressure are
8 probably very important with this disease.

9 DOCTOR NISSEN: Yeah, it's very typical,
10 isn't it, when you give a vasodilator in this setting
11 that you see at least as much effect by increasing
12 flow as you do by decreasing pressure?

13 One of my questions, which relates to the
14 relative efficacy in the different syndromes, there
15 probably were not enough scleroderma patients here to
16 analyze, but if there are any I would be very
17 interested in knowing whether this effect was similar
18 in the scleroderma induced group as it was in the
19 primary pulmonary hypertension group.

20 DOCTOR KORBIN: In the 351 study, we had
21 very few scleroderma patients. It's very difficult to
22 comment on this.

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1 DOCTOR NISSEN: Yes, it would have been
2 very helpful, because, obviously, they would be
3 expected to be much more sclerotic and much more
4 resistant to these effects, but in terms of clinical
5 indication it would be helpful to know if the
6 scleroderma patients - I know they responded
7 clinically with the walk test, but I would be
8 interested in the hemodynamics.

9 DOCTOR RUBIN: One point I should make,
10 perhaps, to remind you, these are all patients who are
11 class 3 or 4 in the two studies, in the 351 all class
12 3, despite conventional therapy. So, these are, by
13 definition, individuals who are not vasoreactive,
14 whether it's PPH or scleroderma they are not
15 vasoreactive. So, these effects are not, at least
16 immediately I think, vasodilatory.

17 DOCTOR KORBIN: Maybe if we can see slide
18 37, I think one of the important things that I have
19 learned from our experts is that there is a very good
20 correlation between the hemodynamics and the walk
21 test, and what we can see, again, in the scleroderma
22 patients the effect was very similar to what was seen

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1 in primary pulmonary hypertension, indicating, at
2 least, although again it is a small number, that we
3 might see the same thing with scleroderma patients.

4 ACTING CHAIR BORER: JoAnn, did you have
5 any additional questions before we move on down the
6 table?

7 DOCTOR LINDENFELD: Let me just ask, I
8 understand in 352 that the original design was to
9 include 150 patients?

10 DOCTOR KORBIN: That's correct.

11 DOCTOR LINDENFELD: And, there's about 230,
12 I think.

13 DOCTOR KORBIN: Two hundred and something.

14 DOCTOR LINDENFELD: So, how did - where did
15 those come from, and how was that -

16 DOCTOR KORBIN: This is a very interesting
17 situation, because when we reached even 140 patients,
18 and we informed the investigators the study has to be
19 stopped, it was tremendous, in a couple of weeks the
20 investigator pushed patients into the trial because
21 they didn't want them to lose the opportunity to go
22 into the trials. And, we couldn't stop them. We got

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1 phone calls, and requests, and you can't believe it,
2 until we were able to stop the trial.

3 ACTING CHAIR BORER: Ray, did you have a
4 question or a comment?

5 DOCTOR LIPICKY: Two questions, actually.

6 We must have failed to urge you to do
7 population kinetics in these two trials, and you
8 didn't think of doing that either?

9 DOCTOR KORBIN: No, we did not implement it
10 in these trials.

11 DOCTOR LIPICKY: Was there some reason that
12 you failed to think about that, as well as we?

13 DOCTOR KORBIN: We failed to think about
14 it, but, in fact, one of the reasons is that we didn't
15 want to complicate even more what the patients are
16 going through in these trials.

17 DOCTOR LIPICKY: Right.

18 DOCTOR KORBIN: This was the main reason.

19 DOCTOR LIPICKY: Okay, that's fine.

20 And then, I can't remember how we allowed
21 you to only look at 125 and 250 mg.

22 DOCTOR KORBIN: In fact, this was your

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1 suggestion. We wanted at first to do only the 125 mg
2 twice a day.

3 DOCTOR LIPICKY: So, we got you to go twice
4 as high.

5 DOCTOR KORBIN: You asked us to do the 250
6 mg twice a day.

7 DOCTOR LIPICKY: We didn't ask you to go
8 ten times as high?

9 DOCTOR KORBIN: No, but we do have, by the
10 way, in fact, eight times higher, and we did in the
11 safety, we gave 2 rounds per day to patients.

12 DOCTOR LIPICKY: Okay, fine.

13 DOCTOR KORBIN: For the safety.

14 ACTING CHAIR BORER: You know, in this
15 regard, although those questions are obviously going
16 to come up again, in the FDA review there's a non-mem
17 analysis of dose effect, which suggests that there
18 really is not much change from 125 to 250, or from
19 62.5 to 250. But, we'll, obviously, hear more about
20 that.

21 Alan?

22 DOCTOR HIRSCH: Well, maybe we'll hear more

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1 about that later. I was going to ask the same
2 question, without blaming Ray and say in the drug
3 development program, you know, were you really
4 considering looking at a higher dose range,
5 substantially higher human range, to see if we could
6 both see greater efficacy?

7 DOCTOR KORBIN: The reason why we didn't go
8 higher is really related to the other programs that we
9 were studying. Once we have seen that 500 mg twice a
10 day was associated with a high percentage of increase
11 in liver enzymes, and we knew from hemodynamic studies
12 in patients with hypertension and CHF that it is
13 plateauing already at the 100/125 mg dose it was
14 decided that this is the highest effective dose from
15 a hemodynamic point of view, and these higher doses we
16 see increased incidence of - liver transferases, we
17 thought that the best dose for these patients would be
18 125 mg twice a day, and we also explored 250 mg twice
19 a day and, indeed, we saw slightly more efficacy with
20 250, but not very impressive.

21 ACTING CHAIR BORER: By the slide you
22 showed us and the data that were shown here and the

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1 data I just quoted, I think that it's hard to say that
2 there was more efficacy at 250.

3 DOCTOR KORBIN: I agree.

4 ACTING CHAIR BORER: In fact, there was a
5 baseline shift, at four weeks you saw greater effect
6 on 62.5.

7 DOCTOR KORBIN: Yes, I think that it looked
8 that the 250 was slightly better than 125, and this is
9 possible.

10 ACTING CHAIR BORER: Okay.

11 Alan, did you have any other issues to
12 raise? No?

13 Paul?

14 DOCTOR ARMSTRONG: No.

15 DOCTOR BREM: With an increase in cardiac
16 output which you demonstrated on the slide, was there
17 a concomitant change in systemic blood pressure or
18 vascular resistance in these patients?

19 DOCTOR KORBIN: I will show it when we come
20 to the safety. We looked into it very carefully,
21 because this is a vasodilator, and what I can tell you
22 now that we didn't see any significant effect, but

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1 I'll show you the data on the safety presentation.

2 DOCTOR BREM: Were these patients having
3 any evidence of systemic elevation in blood pressure
4 before? In other words, were any of them
5 hypertensive?

6 DOCTOR KORBIN: No.

7 DOCTOR BREM: Or, mildly hypertensive?

8 DOCTOR KORBIN: No. The mean systolic
9 blood pressure was about 118/120 ml mercury.

10 ACTING CHAIR BORER: Okay, Tom?

11 DOCTOR FLEMING: Could we go to what for us
12 is your labeled slide 42, incidence of clinical
13 worsening?

14 DOCTOR KORBIN: Yes.

15 DOCTOR FLEMING: While you are going to
16 that I wanted to compliment you on your very
17 informative and organized presentation. It answered,
18 essentially, all of my questions.

19 I did want to follow up on this. Some of
20 us might, in looking at this slide, in particular want
21 to focus on the first three of the four subcategories,
22 the death, hospitalization and discontinuation for

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1 worsening PAH. It may well be that we are still,
2 essentially, looking at 14 events versus nine. Could
3 you tell us if we drop the epoprostenol group,
4 essentially, two questions, is it still 14 versus
5 nine, and what is the log rank analysis when you only
6 have the first three categories?

7 DOCTOR KORBIN: The first question, no one
8 met the epoprostenol criteria on its own.

9 DOCTOR FLEMING: Right.

10 DOCTOR KORBIN: It was always related to
11 worsening PAH, and you can see that, in fact, patients
12 could be in several categories.

13 DOCTOR FLEMING: Right.

14 DOCTOR KORBIN: So, epoprostenol was not on
15 its own.

16 DOCTOR FLEMING: So, the first answer is,
17 yes, it is still 14/9.

18 DOCTOR KORBIN: Yes.

19 DOCTOR FLEMING: Second question is, what
20 does the log rank analysis show when you look at time
21 to first event, when you only include the first three
22 categories?

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1 DOCTOR KORBIN: The first - which
2 categories?

3 DOCTOR FLEMING: i.e., if you don't
4 consider epoprostenol as an event.

5 DOCTOR KORBIN: In fact, it doesn't have to
6 be considered because it's not part of it.

7 DOCTOR FLEMING: Well, we still have the
8 same number of people with events, but it could have
9 been the first event in some people, so the log rank
10 analysis could change.

11 DOCTOR KORBIN: No, it didn't happen, it
12 was always followed.

13 DOCTOR FLEMING: It always followed.

14 DOCTOR KORBIN: Yes, it was first worsening
15 and then epoprostenol, so the worsening was the first
16 event.

17 DOCTOR FLEMING: Okay.

18 So then, in fact, the log rank would still
19 be the same.

20 DOCTOR KORBIN: Yes, exactly the same.

21 ACTING CHAIR BORER: Okay.

22 Let's go on to discussion of safety.

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1 DOCTOR KORBIN: Okay.

2 Well, the safety database is quite
3 comprehensive, and I would really like to spend some
4 time with you in order to explain the different
5 studies that were done with bosentan and, hopefully,
6 this will give us a better understanding why we
7 combined all the patient populations in our safety
8 database.

9 We have seen the studies in patients with
10 pulmonary arterial hypertension, the 351 and the 352
11 with their extensions. There was an old exploratory
12 study called 884 that was done in seven pulmonary
13 arterial hypertension patients. In this study, high
14 IV bosentan was given to these patients, 500 mg, and
15 then they were randomized to either receive placebo,
16 three patients, or bosentan, four patients, at 2,000
17 milligram a day. However, this study was stopped
18 prematurely after two patients that were assigned to
19 placebo died.

20 The second indication that we are pursuing
21 with bosentan is congestive heart failure. There were
22 some older studies that were done, an open label

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1 study, two placebo controlled double blind studies
2 with 2,000 mg a day. But, one of the main studies of
3 this program was the rich 15, NC-15462, where patients
4 received 500 mg,twice a day. This study was stopped
5 prematurely because of the increased incidence of
6 elevated liver aminotransferases, and also because it
7 was decided at that moment that the further program
8 will go on with 125 mg twice a day in CHF patients
9 and, indeed, the open label extension was with 125 mg
10 twice a day in 86 patients.

11 The largest trial in this indication is
12 the ENABLE trial, which is still ongoing. There are
13 1,600 patients in this trial, it is still double
14 blind, and for our sake of discussion today, and it
15 will mainly come during the discussion of the liver
16 enzymes, we assigned all cases of liver enzymes as if
17 they were kept on bosentan and zero on placebo for the
18 purpose of discussion related to this trial.

19 There was one dose finding study in
20 patients with essential hypertension. Here we gave
21 doses of 100, 500, 1,000 and 2,000 mg per day to the
22 patients, it was 50 patients per group.

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1 And, the last study was a proof of concept
2 study in patients with sub - hemorrhage in 30 patients
3 where 1,500 mg per day was given to these patients.

4 So, if you look at what we have in our
5 database, I mentioned the pharmacology studies where
6 we had 434 patients treated with bosentan, we have
7 eight placebo controlled studies, and we see the
8 number of patients, and three open label studies, two
9 of which are extension of the placebo controlled
10 studies.

11 I mentioned the ENABLE trial with the
12 randomization of 1/1, 1,600 patients, so overall if we
13 assume that half of the ENABLE patients are on
14 bosentan we have currently 1,500 patients treated with
15 bosentan. In addition, we have 62 pulmonary arterial
16 hypertension patients coming from study 352 who were
17 treated with placebo which are now in the open label
18 trial.

19 If we look at it in a different way on the
20 eight placebo controlled studies, this is what we
21 have. Patients with pulmonary arterial hypertension
22 and congestive heart failure was about 70 percent of

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1 the patients on these placebo controlled trials. What
2 is interesting, that 60 percent of the patients were
3 treated with doses which were four to eight times
4 above the doses that we are recommending for patients
5 with pulmonary arterial hypertension.

6 The exposure in these trials, not
7 including ENABLE, and not including the open label
8 354, is as follows. In the eight placebo controlled
9 studies and the three open label studies, the exposure
10 was for six months 141 patients, for one year 88
11 patients. In the placebo controlled studies, the mean
12 duration was 85 plus or minus 60/40. This drop that we
13 see here is related to the hypertension study where
14 200 patients treated with bosentan completed the four
15 weeks of treatments compared to 50 patients on
16 placebo.

17 So, what kind of – and the main conclusion
18 that I will show you on the general safety really
19 coming from the placebo controlled trials, and this is
20 the patient demographics of these trials. It was
21 about 57 to 60 percent men, the age about 57, weight
22 77, 90 percent White, and about 30 percent were

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1 studied in the U.S.

2 Now, we looked at the different adverse
3 events, as you have seen the database is quite
4 complicated, so we looked at it by indication, by
5 dose, by treatment duration, in order to find out what
6 adverse events are really drug related. And, what we
7 found out that, in fact, five adverse events were more
8 frequent on bosentan than on placebo, with a
9 difference of at least 2 percent. Flushing, leg
10 edema, abnormal hepatic function, headache and anemia,
11 all of which were found to be dose related.

12 In contrast, we looked at other
13 interesting specific - of specific interest are dose
14 event, cardiac failure, dyspnea, and aggravated PAH
15 because these are related to the indications that we
16 are studying.

17 As a part of it later, we looked at
18 potential for ischemic effect. We looked at different
19 symptoms that might be related to hypertension. We
20 looked at symptoms that could be related to hepatitis,
21 like abdominal pain, nausea and vomiting, and, in
22 fact, all of these adverse events in the placebo

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1 controlled trials were more frequent on placebo.

2 One specific event that we looked for was
3 worsening heart failure. This is because in the rich
4 15, in patients with severe CHF, we have seen an
5 increased incidence of worsening heart failure during
6 the first month of treatment. We explored this
7 observation and we found out that this could have been
8 related to either the starting dose of 125 or 250 mg
9 twice a day or the speed of - titration to the target
10 dose of 50 mg twice a day which was increased weekly.
11 And, indeed, because of this observation in further
12 trials in CHF and pulmonary arterial hypertension it
13 was decided to start treatment with 62.5 mg twice a
14 day and only after four weeks to go to 125 mg twice a
15 day.

16 Now, in this trial, when patients were
17 followed beyond the first month of treatment, in fact,
18 there was - it was reversed, and overall the incidence
19 of hospitalizations with heart failure were
20 significantly lower with bosentan patients compared to
21 placebo.

22 We also looked at this adverse event in

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1 the placebo controlled trials, in the CHF trials, and
2 it was more frequent among the placebo treated
3 patients.

4 What about pulmonary arterial hypertension
5 patients? Again, the first three events are the same
6 as we've seen in the placebo controlled trials. We
7 also have seen nasopharyngitis and hypertension,
8 slightly more frequent in patients with pulmonary
9 arterial hypertension. And, I will come to this point
10 when I will talk about vital signs.

11 Now, what we've seen in the placebo
12 controlled studies, there were quite a number of
13 adverse events that were more frequent on placebo by
14 at least 2 percent compared to the frequency on
15 bosentan.

16 What about adverse events that led to
17 withdrawal? Well, the main reason in bosentan was
18 abnormal hematic function, 4.1 percent of the
19 patients. The second most frequent was headache, 1.2
20 percent of the patients, but this occurred mainly at
21 very high doses of bosentan. In patients with
22 pulmonary arterial hypertension we see that the

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1 dropout was higher among the placebo patients, 10
2 percent versus 5.5 percent, and again, the different
3 reasons are here, and there was no one specific reason
4 that it was more frequent on bosentan, interestingly,
5 7.5 percent of the patients on placebo dropped because
6 of aggravated pulmonary arterial hypertension.

7 What about the reasons for death in the
8 eight placebo controlled studies? The overall
9 frequency was similar, both in placebo and on
10 bosentan, and again, there were very few deaths on a
11 specific reason. In one case, it was more frequent on
12 placebo, and in another case on bosentan, but most of
13 these cases occurred in the CHF trial, but overall
14 there was no difference between the groups.

15 When we look at patients with pulmonary
16 arterial hypertension, again, the overall frequency
17 was similar, and the most frequent adverse event was
18 in two patients, two in placebo for aggravated PAH,
19 both CHF and bosentan.

20 Now, I mentioned before the vital signs,
21 and, indeed, we look at what is happening in placebo
22 controlled studies and in the pulmonary arterial

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1 hypertension studies. And, we can see that first of
2 all heart rate on bosentan patients did not change, or
3 maybe even tended to slightly decrease. Systolic and
4 diastolic blood pressure slightly decreased, and it
5 was dose related, but it's very difficult to assess it
6 when you look at treatment and end of treatment, so we
7 looked at the incidence of a decrease in systolic
8 blood pressure to less than 80 at any time during
9 treatment in the placebo controlled studies and also
10 the adverse event hypertension.

11 In the placebo controlled studies, it was
12 slightly more frequent on placebo than bosentan. In
13 the pulmonary arterial hypertension studies, it was
14 slightly more frequent on bosentan. We looked at each
15 one of these patients, and in all of these patients it
16 was mild, it was transient, and it never resulted in
17 premature discontinuation of any pulmonary arterial
18 hypertension patient.

19 Now, one of the things that we know from
20 other drugs for this disease is the potential for
21 rebound. Now, we have limited experience on this
22 issue. In 22 pulmonary arterial hypertension

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1 patients, who were discontinued during the trials and
2 we could have data on them because they were not put
3 on epoprostenol, there were five patients that had
4 treatment discontinued after dose reduction, seven
5 that were interrupted for two to 14 days, and ten
6 patients in the open label trial, 354, the extension
7 of the large trial, that were discontinued. In none
8 of these patients there was an acute rebound observed.
9 Only one patient had aggravated pulmonary arterial
10 hypertension and this occurred 29 days after
11 discontinuation.

12 We also looked at potential rebound in
13 hypertensive patients and CHF patients who were
14 treated with 2 grams per day and treatment was stopped
15 abruptly at the end of the trials, and there was no
16 evidence for rebound.

17 The other questions that we ask ourselves,
18 what is happening to patients who are going to
19 epoprostenol after stopping treatment or not stopping
20 treatment? There were eight ex-placebo patients who
21 were started on epoprostenol, five improved, one died,
22 and two got worse. Eight ex-bosentan patients were

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1 started on epoprostenol, five improved, two died, and
2 one got worse. And, in six patients epoprostenol was
3 added on top of bosentan, five improved and one died.
4 At least, although this is limited, at least we see
5 here that patients still had the opportunity to
6 improve if they had to be discontinued from bosentan,
7 if they are being put on epoprostenol.

8 What about the long-term experience in
9 patients with pulmonary arterial hypertension? Study
10 353, the extension of 351, there were 29 patients, and
11 remember their disposition, and the exposure was 485
12 days plus or minus 97 days, and this is the range.
13 Twenty-eight patients were treated for at least one
14 year. There were no deaths in this trial. One
15 patient discontinued because of pulmonary arterial
16 hypertension, and four patients had to be up titrated
17 to 250 mg twice a day after a year or year and a half
18 of treatment because of slight deterioration in their
19 symptoms. And, indeed, their symptoms improved when
20 they went to the higher dose here.

21 In the 354 trials, we know that 200
22 patients went into this trial. Currently, up to 31st

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1 of May, and, you know, this trial is ongoing and we
2 tried to give as much information as we can on these
3 trials, there are 200 patients in this trial coming
4 from the 352 trial, 62 ex-placebo and 138 ex-bosentan,
5 and we see the mean treatment duration. One hundred
6 patients are treated for at least six months. During
7 this period, there were two days, because of pulmonary
8 hemorrhage, two discontinuation for worsening
9 pulmonary arterial hypertension, six were discontinued
10 because of elevated enzymes, and four were
11 discontinued either because of adverse events or
12 administrative reasons.

13 So, we looked at the overall exposure of
14 these patients in the four trials, and this is the
15 overall exposure of these pulmonary arterial
16 hypertension patients. And, we can see that for six
17 months there are about 128 patients, for 12 months 28
18 patients.

19 Now, we accounted, we looked at every
20 patient that was in this trial, and we accounted for
21 everyone that dropped from the trial up to 31st of
22 May. We tried to look what would be the survival of

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1 at least this group of patients and this is what we
2 have seen in this group of patients. This is the
3 fitted exponential, and based on this it is predicted
4 that the one year survival is going to be 95 percent.

5 There were no relevant differences between
6 bosentan and placebo when it comes to serious adverse
7 events, no relevant changes on ECG parameters or
8 treatment emergency findings, and there were no
9 relevant changes on laboratory tests, except a
10 decrease in red blood cell parameters and an increase
11 in liver enzymes, and this is where I would like to
12 move now in my presentation.

13 Let me start with the hemoglobin
14 concentration. What have we seen in preclinical
15 studies? There was a mild decrease, 7 to 13 percent
16 in hemoglobin concentration in rats and dogs. There
17 was no evidence for hemolysis, immunoallergic
18 reaction, bone marrow toxicity or bleeding. However,
19 there was evidence for increased plasma volume with
20 hemodilution in rats.

21 What have we seen in patients? And, we
22 have looked at it in different aspects. The change

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1 from baseline in hemoglobin concentration to end of
2 treatment or the lowest value, and different magnitude
3 of decrease in hemoglobin concentration. We can see
4 that there was a decrease of 0.8 gram/deciliter, if
5 you look at end of treatment all the lowest value. 57
6 percent of the patients had a decrease by at least 1
7 gram/deciliter on bosentan, and 29 percent on placebo,
8 with a treatment effect of 28 percent.

9 A decrease below the lower limit of
10 normal, the treatment effect was about 7.5 percent,
11 indicating that most of these patients still remained
12 within normal limits.

13 A marked decrease in hemoglobin by more
14 than 15 percent to less than 11 gram/deciliter was
15 observed in 2.6 and 5.6 percent of the placebo and
16 bosentan patients, respectively.

17 A larger decrease, no difference between
18 placebo and bosentan, in fact, a larger decrease was
19 always related, could be related to a very clear
20 reason, it could be bleeding, renal failure, or other
21 reasons, and there was no difference between the
22 groups.

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1 Looking at patients with pulmonary
2 arterial hypertension, the picture was practically
3 similar.

4 This value had different indications, it
5 seems that the decrease in patients with hypertension
6 was smaller compared to patients with CHF and patients
7 with pulmonary arterial hypertension. Now, this could
8 be related to the fact that these patients were
9 treated only for four weeks compared to a longer
10 duration in this patient population, but also, and we
11 will come to this when we talk about the mechanism, it
12 could be related to the fact that patients with CHF
13 and PH have volume retention and they tend to have
14 slightly increased levels of erythropoietin.

15 When we looked at the patients with
16 pulmonary arterial hypertension who had a decrease in
17 hemoglobin, there was no evidence for increase in
18 bilirubin, no associated decrease in white cells or
19 platelets, no increase in - above the upper limit of
20 normal, and no premature withdrawals due to anemia.
21 Blood transfusions had to be given to four patients.
22 One had severe epistaxis, two GI bleeding, and one had

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1 anemia, the later ones it was found out to be -
2 positive and - anemia.

3 In all eight placebo controlled studies,
4 1.8 percent of the bosentan patients and 1 percent of
5 the placebo patients had to get blood transfusions.

6 Now, when these occurred, and again, you
7 can see the different criteria, what is interesting
8 that the decrease by at least 1 gram mainly occurred
9 in the first four weeks of treatment, and then the
10 decrease is parallel between placebo and active
11 treatment. Most of the cases of mild decrease in
12 hemoglobin occurred within the first 16 weeks of
13 treatment, and there was no difference when the
14 decrease was to a larger extent.

15 Looking at the time course, and this is
16 interesting because we had opportunity to look at
17 patients in the rich 1 trial and this open label
18 extension. When you start bosentan there is already
19 at week three a decrease in hemoglobin, slightly more
20 at week 12, and then it tends even to come to be
21 stabilized, definitely no progressive decrease, and
22 nothing happened on placebo.

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1 When you stop treatment, it comes back to
2 baseline very fast. You start treatment, it goes back
3 to the same level, and also the ex-placebo patients go
4 to the same level.

5 In patients with pulmonary arterial
6 hypertension, the same picture, after four weeks of
7 treatment there is a slight decrease in hemoglobin and
8 it stabilizes and does not go down progressively.
9 Clearly, we have a stabilization.

10 Now, looking at different reasons that
11 could explain it, we couldn't find evidence for
12 hemolysis. There was no increase in bilirubin and no
13 increase in reticular size and MCV, this is mainly
14 coming from data that we are exploring in the ENABLE
15 trial for every patient who had a decrease in
16 hemoglobin concentration. No evidence for bone marrow
17 toxicity, because there was no marked decrease in
18 white blood cells and platelets concomitantly, and for
19 two patients where we have bone marrow we found out
20 that all the three lines were normally represented.
21 And, there was no evidence for bleeding tendency,
22 there was no evidence for bleeding in most cases.

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1 What is the mechanism? We believe that it
2 could be hemodilution – this is based on preclinical
3 evidence of increased plasma volume, it is compatible
4 with the clinical picture, and it is compatible with
5 the mechanism or faction of the drug, vasodilation, we
6 know that other vasodilators also reduce hemoglobin
7 concentration, and a decrease in capillary
8 permeability.

9 I mentioned before erythropoietin, it is
10 possible that in patients with pulmonary arterial
11 hypertension better oxygenation of the tissues, and in
12 patients with heart failure, again, better oxygenation
13 and better renal blood flow could result in a decrease
14 in the elevated erythropoietin in these patients, and
15 maybe this is why in patients with pulmonary arterial
16 hypertension and CHF the decrease is larger, compared
17 to patients with hypertension.

18 How to deal with this observation? Well,
19 we think that the risk to the patient is small.
20 Hemoglobin concentration should be evaluated after one
21 and three months. And, in case there are cases of
22 mild decrease in hemoglobin concentration, another

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1 reason should be looked for, and if treatment needed
2 this should be based on clinical judgment.

3 I would like to move now to the liver
4 observations. Preclinical studies have shown that
5 there is evidence for core studies, this is based on
6 increase in plasma bile salt and alkaline phosphotase,
7 and an increase in liver aminotransfers was observed
8 only transiently in dogs. There was no evidence for
9 reactive or toxic metabolites, immune or allergic
10 reaction, centrolobular necrosis or - drug toxicity.

11 There was, however, some evidence for
12 competitive inhibition of bile salt excretion, which
13 can lead to accumulation of bile salt and hepatic -.

14 What about patients? Here we see the
15 different indications, pulmonary arterial
16 hypertension, CHF and hypertension, and the different
17 doses. The overall here dose, and the overall here
18 their indication. And, we can clearly see that there
19 was a clear tendency for dose relationship. The only
20 real dose finding study in hypertension showed very
21 clear dose relationship, although the treatment here
22 was only four weeks.

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1 Looking at the severity of the increase,
2 this is based on an increase of more than – between
3 three to five times the upper limit of normal, five to
4 eight or more, than eight in pulmonary arterial
5 hypertension patients, other indications, all the
6 patients, and again, looking at ENABLE. Assuming that
7 all cases occurred in patients on bosentan, and this
8 was the incidence. What we can see is an increase of
9 more than eight was about 4 percent of the patients.

10 Now, not only the incidence was dose
11 related, but it seemed that the severity could be dose
12 related, and we can see here in the pulmonary arterial
13 hypertension based on 125 twice a day and 250 twice a
14 day, that reports of adverse events of hepatic
15 function of normal was 4.2 and 14.3 percent of the
16 patients. Maybe this is a reflection of what the
17 investigator thought about the severity. More than
18 three times the upper limit of normal, 11 versus 14
19 percent. More than eight times the upper limit of
20 normal, 2 versus 7 percent.

21 Now, more patients on the lower dose, 125
22 mg, tended to have transient elevation, meaning that

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1 the elevation disappeared when treatment continued,
2 eight versus four, and three patients had to be
3 discontinued from the higher dose because of the
4 elevation of liver enzymes.

5 When we looked at the time course, there
6 was a gradual increase over several weeks, and in many
7 patients it normalized while treatment continued, and
8 this tended to be dose related. 70 percent with the
9 125, 40 percent with the 250, and 16 percent with the
10 500. There was complete resolution if treatment was
11 discontinued.

12 When the resolution occurred? Well, in
13 most patients, based on the safety database, ENABLE
14 cases and the open label extension trial within 23 to
15 32 days, and we see the range, the range that we see
16 here. 97 percent of the elevations were resolved
17 within eight weeks. The 3 percent that is missing
18 here occurred on week nine.

19 Were there any predisposing factors for
20 the elevation? Well, if the patient had liver
21 aminotransferases above the upper limit of normal at
22 baseline, the incidence increased to 16.5 percent

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1 compared to 10 percent. If alkaline phosphotase was
2 elevated at baseline it had no effect.

3 Looking at different concomitant
4 indications, we found out that concomitant
5 administration with glibenclamide, where there is no
6 pharmacokinetic interaction, was associated with the
7 higher incidence. This could be related to the fact
8 that glibenclamide and bosentan both inhibit the bile
9 salt excretion part. There was no effect of age or
10 gender on this observation.

11 When did it occur? More than 90 percent
12 of the patients within the first 16 weeks of treatment
13 in the placebo controlled studies and in the pulmonary
14 arterial hypertension. The same observation was in
15 the ENABLE trial, and we can see again the incidence
16 in ENABLE up to 72 weeks of follow up, and most of the
17 cases occurred initially.

18 Now, the increase in liver enzymes is
19 typically unsymptomatic. In some patients there were
20 associated symptoms, and we looked specifically for
21 these associated symptoms. We looked for nausea,
22 vomiting, abdominal pain, fever, jaundice or an

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1 increase of bilirubin at least for more than three
2 times the upper limit of normal. And again, in most
3 of these - in many of these patients it could be
4 related or not, and what is important is maybe these
5 three patients that I will talk a little bit more
6 later on, and this was the observation in the placebo
7 controlled studies, the open label studies and in
8 ENABLE.

9 What is the type of liver injury? When we
10 use the criteria for the Council of International
11 Organization of Medical Science, and this is based on
12 the ratio between the increase in ALT and the increase
13 in alkaline phosphotates related to the upper limit of
14 normal. If the ratio is less than two, it is regarded
15 as cholestatic, more than five hepatocellular, between
16 the two mixed.

17 What have we seen, is that in most
18 patients it was either hepatocellular or mixed, both
19 in the placebo controlled studies and in the ENABLE
20 trials.

21 What is the mechanism? It's not yet fully
22 elucidated. Competitive inhibition of bile salt

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1 excretion may be a contributory factor. There is no
2 evidence for immunoallergic reaction during treatment
3 or at reintroduction. So, how can we assess the risk
4 associated with this increase in liver
5 aminotransferases? We looked at the suggestions of a
6 Doctor Hyman Zimmerman. What he said is, that there
7 is an increased risk of acute liver failure in
8 patients with predominantly hepatocellular disease if
9 they have this combination, an increase in liver
10 aminotransferases more than three times the upper
11 limit of normal, associated with clinical jaundice,
12 with small changes in alkaline phosphotase. And, if
13 you have this combination, 10 percent of the patients
14 might develop severe injury or acute liver failure in
15 this combination.

16 Now, we looked at, in all our databases,
17 especially in our long-term trials, and let me show
18 you here, this is the pulmonary arterial hypertension
19 trial, this is the rich one with its extension, and
20 this is the ENABLE trial, and what we see here is that
21 at least we can look at up to 12 months of treatment.
22 We have 28, 61 patients in these groups, and half of

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1 these 1,000 patients in the ENABLE group, and we can
2 go also to one and a half years and see the numbers.

3 And, this is important because in all
4 these databases, we haven't seen any case of acute
5 liver failure. There were three patients who had an
6 increase in liver enzymes and bilirubin more than
7 three times the upper limit of normal, but they also
8 had an increase in alkaline phosphatase of two to
9 three times the upper limit of normal, so they didn't
10 really meet the Zimmerman criteria.

11 If they didn't have the increase in
12 alkaline phosphatase, and if we assume that all the
13 cases are drug related, and we implement the Zimmerman
14 criteria then we can say that there are three out of
15 1,500 patients exposed to bosentan, not including the
16 pharmacology studies, which means one in 500.

17 In this respect, one can assume that
18 theoretically in the worst case it could happen maybe
19 in one in 5,000 patients, but this is really in the
20 worst case.

21 In all these three cases, the increase in
22 liver enzymes and bilirubin disappeared completely

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1 after treatment cessation within 24 to 64 days, based
2 on evaluation data.

3 Let me summarize this liver observation.
4 Overall, the incidence 11.2 percent. The incidence
5 and severity dose related. The onset is during the
6 first 16 weeks of treatment. There is a gradual
7 increase over several weeks, and it is transient,
8 meaning that it disappeared with continued treatment
9 in 50 percent of the patients. It's typically
10 asymptomatic.

11 In 50 percent of the patients, there is an
12 increase in alkaline phosphatase, and infrequently one
13 may see an elevated bilirubin.

14 Rapid and complete resolution was observed
15 with treatment cessation, and there was no evidence
16 for continued liver injury in any of these patients.

17 So, what can we do in order to reduce any
18 risk, any theoretical risk that might occur with these
19 patients? Well, we know that patients with pulmonary
20 arterial hypertension are very compliant and they are
21 treated with very dedicated group of physicians
22 because of the severity of their disease. And, we

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1 expect that the compliance here will be very high.

2 We are going to implement recommendation
3 of monthly monitoring for the first six months, and,
4 of course, before treatment monthly monitoring, and
5 then quarterly thereafter, and this monitoring can be
6 incorporated into the routine management of these
7 patients, where we measure INR and chemistries. And,
8 there are strict guidelines for what to do when you
9 have an increase in liver enzymes. If the increase is
10 three to five times the upper limit of normal, it has
11 to be interrupted or reduce the dose. If it is more
12 than five, it has to be stopped. If it is any level
13 of increase, and associated with symptoms of liver
14 injury, or increase in bilirubin more than three times
15 the upper limit of normal, it has to be stopped.

16 Education of physicians, nurses and
17 pharmacists is going to be implemented, and
18 information to patients will be distributed directly
19 via drug distribution and through patient
20 organization.

21 Based on all the observations that we have
22 seen up to now on efficacy and safety, the starting

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1 recommended dose is 62.5 mg twice a day for four
2 weeks, followed by 125 mg twice a day. No dose
3 adjustment is needed for most subgroups. Not
4 recommended for patients with moderate to severe liver
5 impairment, patients with baseline elevated liver
6 aminotransferases more than three times of normal,
7 patients on glibenclamide or cyclosporin A and
8 pregnant women.

9 Let me summarize my presentation. Treated
10 with bosentan is associated with improvement in all
11 clinical and hemodynamic efficacy measures, indicating
12 that the daily lives of these patients may improve.
13 There is a reduction in the risk of clinical
14 worsening, indicating or suggesting that maybe the
15 clinical course of the disease may be affected. The
16 drug was very well tolerated up to 2 grams per day,
17 but it is associated with potential risks related to
18 the modest decrease in hemoglobin concentration and
19 the increased incidence of elevated liver
20 aminotransferases, both of which can be managed by
21 appropriate monitoring and education.

22 Let me finish with the sentence that I

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1 started, I hope that we were able to show you that the
2 efficacy or the benefits of the drug outweigh its
3 risks, especially in this disease, for which there are
4 very limited treatment options.

5 And, what I would like before we break for
6 questions, if it's okay with you, Doctor Borer, to get
7 a very short presentation by Doctor Maddrey on the --
8 to put it in context, the increase in liver enzymes.

9 ACTING CHAIR BORER: It's fine, but before
10 we do that I'm sure that many people on the panel will
11 have a number of questions.

12 I want to ask you, before we get off into
13 the specific issue of hepatotoxicity, how did you
14 select the dose to be tested for this drug?

15 DOCTOR KORBIN: In our trials?

16 ACTING CHAIR BORER: Yes, let me tell you
17 where I'm going here, and I think it might be useful
18 if people haven't looked at this to look at the non-
19 mem analysis on page three of the FDA briefing
20 document, which really is not intuitively much
21 different from, even though it's based on a model, the
22 actual data from the sponsor's presentation document,

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1 concerning walking distance over time.

2 The way I look at these data, the non-mem
3 is on page three of the briefing document, you can
4 also have reference to page 64 of the Actelion
5 document, as one of the examples of effect over time,
6 the way I look at these data there really is little,
7 if any, difference in the effect of 62.5 bid, from 125
8 bid, from 250 bid. There may be some, but it's very
9 difficult to say that there is because, of course, we
10 don't have a parallel 62.5 arm bid, arm that went out
11 16 weeks, or 12 weeks, or however many weeks it is.
12 We have here an agent that, you know, clearly is
13 effective, has some potential problems associated with
14 it that we're not going to be able to define here
15 today because of the small size of the population that
16 was tested. JoAnn got into a lot of them earlier, and
17 I won't repeat them, but, you know, we have
18 teratogenicity, the liver problem, modest though it
19 may be, et cetera, et cetera.

20 Why was there no effort to look for a
21 minimally effective dose, or again, how did you select
22 the doses that you used?

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1 DOCTOR KORBIN: Okay.

2 Let me, first of all, explain how did we
3 select the doses, and what did we know about the
4 different doses. If I can see this slide, please.

5 First of all, the selection of these
6 doses. We knew already, before we started the trials,
7 that 100 and 125 mg twice a day were at the top of the
8 hemodynamic dose response, based on a decrease in
9 blood pressure. We also knew that higher doses were
10 associated with increased incidence of elevated liver
11 aminotransferases.

12 So, and based on what I've shown you
13 before about the patients with CHF, it was decided to
14 start with 62.5 mg and after four weeks to go to 125
15 mg twice a day, and based on the advice that we got in
16 the larger study we also started the 250 mg twice a
17 day.

18 Now, in our trials what we have seen, that
19 the 250 mg seems to be slightly better than the 125
20 mg, as I've shown before in the efficacy, slightly.

21 ACTING CHAIR BORER: But again, you didn't
22 show that. You didn't show that, and I think we've

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1 got to get away from that. What you showed was that
2 people who had a big response to 62.5 had – continued
3 to have greater walking distance if they had 250 after
4 that, than people who had less of a response to 62.5
5 had if they were then given 125 bid for the next
6 several months. That's what the data show, they don't
7 show greater efficacy with 250 than with 125.

8 And again, this non-mem analysis is, you
9 know, pretty clear on that point, too. So, I think we
10 can't say at all, in any way, that there's a
11 difference between 125 and 250. Maybe there is, but
12 I don't think we can say that, or even suggest it,
13 from these data.

14 And, what I'm suggesting here is, I
15 understand how you selected the dose, there's nothing
16 wrong with that. You know, you have to make a guess.
17 You take a gamble, it works, it doesn't work. It
18 worked here, and that's fine. What I'm asking is, is
19 there any intention, do you think it would be a good
20 idea to look for the minimally effective dose, if, in
21 fact, 62.5 really is as good over time, which we don't
22 know, as 125, and 125 is the same as 250, and we get

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1 toxicity that's dose related, wouldn't we want to know
2 if there's a lower dose that works?

3 Remember, what we have here is a set of
4 data that suggest a meaningful and statistically
5 significant effect on various measures of symptoms and
6 activity tolerance. The issue of natural history
7 improvement really we can't deal with from these small
8 numbers, I think.

9 So, wouldn't it be useful to know about
10 the minimally effective dose or the minimal dose that
11 could give you the kinds of benefits that we see here?

12 DOCTOR KORBIN: Let me try to answer this
13 question. Of course, we don't have data, valid data
14 with 62.5 mg. We do have indirect data suggesting
15 that the 62.5 mg is less effective than the 125 mg
16 twice a day. This is based on the magnitude of
17 increase at week four, but, of course, time could be
18 a factor.

19 We also know about the magnitude, I think,
20 within the open label trial, where we saw a 22 meter
21 increase. We also have evidence that when patients
22 went from the 125 to 62.5, when they switched to the

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1 open label before knowing what was the dose, or from
2 250 to 62.5, about 10 percent of the patients
3 developed worsening of symptoms, and as a result the
4 dose had to be increased in order to overcome these
5 observations. So, this is just an indirect
6 observation.

7 And, also I would say that if we look at
8 the mean, and also the median effect on the walk test,
9 and this is what we see on this slide, there was 35
10 meters with the 125 and 54 meters with the 250,
11 suggesting, just suggesting, that the dose response,
12 but maybe not, maybe not.

13 ACTING CHAIR BORER: Yeah, okay. I mean,
14 that's all very reasonable. I think in considering
15 how to move forward with this agent, you really do
16 have to consider the time effect. Steve can discuss
17 this issue with greater clarity than I can, but all
18 the data that are available from various conditions,
19 cardiovascular conditions, in which rehabilitation
20 therapy involving exercise is employed, seem to
21 suggest that exercise breeds the capacity to do more
22 exercise. So, you know, it's really impossible to

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1 deconvolute the effect of time from the effective dose
2 once you go past four weeks here.

3 That's not a pejorative comment, I mean,
4 this is a superb development program, but I think that
5 the data raise some issues, especially when we are
6 talking about the relation of safety and efficacy
7 that, perhaps, you might think about resolving.

8 Before we go on to the liver portion, does
9 anybody have anything else?

10 Paul?

11 DOCTOR ARMSTRONG: Again, I'd like to echo
12 what my colleagues have said, this has been a very
13 lucid presentation of an important agent.

14 I'd like to pursue three or four related
15 issues, and maybe I'll lay them out and then repeat
16 them if that's necessary.

17 Is there a first dose effect?

18 What is the mechanism, in your mind, you
19 articulated some of the issues in aggravation of heart
20 failure early on, but not provided your incite into a
21 potential mechanism.

22 As I look at the briefing document, which

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1 provides us additional incite onto the reasons for
2 death in the placebo versus the bosentan groups, there
3 are some deaths in the bosentan group that are
4 characterized individually as cardiorespiratory
5 arrest, ventricular fibrillation, which don't meet the
6 threshold of greater than three, and, therefore, get
7 into your slide 74.

8 And, as I look at the Kaplan/Meyer curve
9 on the briefing document, page 15, figure 5, it looks
10 to me as though there is an apparent excess in the
11 first three months of deaths with bosentan, and then
12 a crossover and clearly no difference at the
13 conclusion of the observation. So, again, I'm
14 interested in some incites in the early phase of
15 introduction of this agent to patients with heart
16 failure and pulmonary hypertension, and what useful
17 information might be derived vis-à-vis its ultimate
18 application.

19 DOCTOR KORBIN: Let me try to answer.

20 First of all, regarding the Kaplan/Meyer
21 curve that you see in the book, the difference within
22 the groups is only related to heart failure and not to

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1 death. The deaths in the first month of treatment was
2 four in the placebo, one on the low dose and four on
3 the high dose. The difference was really because of
4 hospitalization, for heart failure.

5 We looked at these patients very
6 carefully, and in many of them it was slight worsening
7 of heart failure, they were hospitalized, diuretic
8 treatment was increased, they got better, they left
9 the hospital. This was the main observation.

10 Now, what could be the reason, maybe fluid
11 retention. When you start high and you go too fast,
12 this is why we decided to go to 62.5, wait four weeks
13 before we go to the 125, and, indeed, in patients with
14 pulmonary arterial hypertension we haven't seen any
15 worsening of heart failure during this period.

16 So, from this point of view, I think that
17 this was also the reason for the dosing regiment and
18 the observations related to this aspect.

19 DOCTOR ARMSTRONG: Is there a first dose
20 effect? Do you see, as sometimes in the case -

21 DOCTOR KORBIN: No.

22 DOCTOR ARMSTRONG: - with ace inhibitors,

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