

1 a profound hypertension?

2 DOCTOR KORBIN: No. We looked into these
3 to see if there were any - hypertension, hypertension,
4 syncope, dizziness, as a result of first dose effect,
5 and there was no difference from placebo. We looked
6 at it in patients with heart failure and also in
7 patients with pulmonary arterial hypertension, there
8 was no evidence for first dose effect.

9 ACTING CHAIR BORER: Ray?

10 DOCTOR LIPICKY: Just coming back to the
11 point you were making, Jeff, I asked the sponsor if he
12 could remember why we failed to convince him to do
13 dose ranging, but I forgot to ask Doctor Temple if he
14 remembered why we failed to do our job.

15 DOCTOR TEMPLE: No, I don't remember, but
16 it's possible there were hemodynamic data that
17 convinced us.

18 DOCTOR LIPICKY: Well, but, obviously, that
19 was an error, right? Retrospectively, that was a
20 mistake.

21 DOCTOR TEMPLE: Maybe.

22 DOCTOR LIPICKY: To be convinced by that

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1 was retrospectively a mistake, because now we are
2 stuck with only having a twofold dose range explored,
3 and having clear dose related side effects, and not
4 having a very good data set, although this is, I must
5 say, an elegant piece of work, but not having a good
6 enough data set to begin to make decisions.

7 DOCTOR TEMPLE: I think you know not to go
8 higher. Ray, I think you know not to go higher. The
9 main question is -

10 DOCTOR LIPICKY: Oh, from what?

11 DOCTOR TEMPLE: - well, first of all, when
12 you do, you get more side effects, and second, it
13 doesn't look like there's much of an effect, either by
14 the -

15 DOCTOR LIPICKY: The only side effect here
16 is liver.

17 DOCTOR TEMPLE: Yeah.

18 DOCTOR LIPICKY: We didn't know that at the
19 time we were talking about it.

20 DOCTOR TEMPLE: Oh, no, no, we may not have
21 been wise enough before, but now, in retrospect -

22 DOCTOR LIPICKY: Right, so how would we

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1 know that you shouldn't go higher?

2 DOCTOR TEMPLE: - it would be hard to be
3 enthusiastic for studying much larger doses.

4 DOCTOR LIPICKY: They studied 2,000 in
5 essential hypertension.

6 DOCTOR TEMPLE: Right.

7 DOCTOR LIPICKY: Why did we let them do
8 that there, and not in pulmonary hypertension?

9 DOCTOR TEMPLE: Well, I'm a bottom line
10 guy.

11 DOCTOR LIPICKY: I mean, I'm at a total
12 loss in being able to explain that failure.

13 DOCTOR TEMPLE: Right.

14 But still, the question Jeffrey raised is
15 mostly should we know more about the lower dose.
16 Probably not. Should we know more about the higher
17 dose, because we do have a fairly substantial
18 comparison, and there's no particular enthusiasm for
19 the 250, although with more data you might develop
20 some.

21 And, I guess I wanted to ask whether
22 there's any question of starting with the lower dose

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1 and leaving it, or leaving it if it seemed – if the
2 patient seems to be feeling remarkably better. Any
3 thought about that, or, perhaps, using a period of
4 time to see if there's any liver abnormality and then
5 going up only if there isn't?

6 DOCTOR KORBIN: Well, again, the design was
7 as it was, we didn't plan to go to the 62.5 because we
8 didn't expect that it will be as efficacious as 125,
9 but rather less, and one of the things that we are –
10 which is very obvious to us, that these patients, in
11 reality, let's say, and maybe on this aspect maybe
12 Doctor Rubin might want to comment on this because he
13 treated these patients, he saw the patients where the
14 dose was decreased or increased, and he can say
15 something, but I can say that already the 62.5 we do
16 see cases of increase in liver enzymes, and we don't
17 know if this will be a lower incidence. I think that
18 Doctor Maddrey might touch this issue.

19 And again, remember, we are talking here
20 about an increase in liver enzymes, we still don't
21 know what is the risk associated with it, if at all.
22 So, we might have 10 percent, or 5 percent, or 20

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1 percent, we still don't know what is the risk
2 associated with this.

3 And, Doctor Maddrey will touch this issue
4 in his presentation.

5 ACTING CHAIR BORER: JoAnn?

6 DOCTOR LINDENFELD: You showed us some data
7 on hospitalizations in pulmonary hypertension patients
8 and heart failure, and we saw that hospitalizations
9 were actually slightly less, four pulmonary
10 hypertension in the bosentan patients, and four heart
11 failure in the bosentan patients. What about all-
12 cause hospitalizations?

13 DOCTOR KORBIN: Can we slide again?

14 In fact, what we see here is the all-cause
15 hospitalizations in this study, 352, we see the 4
16 versus 13 percent due to PAH, cardiovascular related,
17 in fact again, it was higher on placebo compared to
18 bosentan, and the overall hospitalization again we can
19 see it was higher on placebo than on bosentan. So, it
20 was consistently more in placebo than on bosentan,
21 either for PAH or for other reasons.

22 DOCTOR LINDENFELD: Okay.

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1 Let me just touch on anemia for a minute.
2 We had data in our briefing document that suggested
3 that in ENABLE there is a data that the reticular site
4 count is depressed in - patients?

5 DOCTOR KORBIN: That's correct, in every
6 patient that had a mild decrease in hemoglobin we
7 asked the investigator to check MCV, MCH, reticular
8 site, and we are watching these patients to see if
9 there was any evidence for hemolysis, and we didn't
10 see any evidence for hemolysis.

11 There was no increase in bilirubin, no
12 increase in reticular sites, and no increase in MCV,
13 in the patients who had a marked decrease in
14 hemoglobin, of course, this is still a blinded study,
15 but assuming that, again, all cases - this is what we
16 are looking at.

17 DOCTOR LINDENFELD: Okay.

18 And, in rich 1, as I understand it there
19 was a drop in white count in the bosentan patients
20 overall, it was 9, 15 and 11 percent at weeks three,
21 12 and 26?

22 DOCTOR KORBIN: There was - in overall,

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1 there was about 8 percent decrease in the mean of
2 white blood count, but there was no associated of
3 marked decrease in white blood cells in the case who
4 had a marked decrease in hemoglobin concentration, and
5 the same thing is true for platelets.

6 So, a marked slight decrease we have seen,
7 maybe it's related to hemodilution, maybe not. I
8 think Doctor Spevak says that it is not related to
9 hemodilution, but no marked decrease in white blood
10 cells concomitant with a decrease in hemoglobin.

11 DOCTOR LINDENFELD: So, these are separate
12 things that need to be monitored, they need to be
13 monitored, I mean, separately, they are not related.

14 DOCTOR KORBIN: The white blood cells?

15 DOCTOR LINDENFELD: Right.

16 DOCTOR KORBIN: I don't think it needs to
17 be monitored, because it didn't go down to levels
18 which are dangerous or marked decrease.

19 DOCTOR LINDENFELD: Okay, there were no
20 drops to dangerous levels.

21 DOCTOR KORBIN: No.

22 DOCTOR LINDENFELD: So, do you know what

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1 the mean drop was, 11 percent, so that's -

2 DOCTOR KORBIN: If we can see the slide,
3 yes, we can see here the mean decrease in white blood
4 cells, and the - no, this were the mean decrease,
5 right, this is the mean decrease, this is the change
6 in platelets in placebo and in bosentan, and these are
7 the cases of marked decrease in hemoglobin in white
8 blood cells concentrations or in platelets, and there
9 was no difference between placebo and active
10 treatment. And, it was not concomitant with the
11 decrease in hemoglobin concentration.

12 DOCTOR LINDENFELD: Okay.

13 And again, we've heard that there's no
14 problem with withdrawal of bosentan, but in patients
15 who had liver function tests five times normal it was
16 recommended to stop?

17 DOCTOR KORBIN: That's correct.

18 DOCTOR LINDENFELD: And, can you tell me
19 something about problems in those patients with more
20 severe pulmonary hypertension? I didn't see that
21 data.

22 DOCTOR KORBIN: We had six patients in the

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1 open label 354 study where treatment was stopped, and
2 also three patients in the 352 study where treatment
3 was stopped because of liver enzymes, and none of them
4 had acute rebound, and none of them needed to go into
5 any specific other treatment.

6 It doesn't mean that they didn't have
7 maybe slightly worsening of dyspnea, because of loss
8 of efficacy, or maybe the walk test could be
9 decreased, but definitely no acute rebound in these
10 patients.

11 DOCTOR LINDENFELD: And, you didn't require
12 hospitalization in those patients -

13 DOCTOR KORBIN: No.

14 DOCTOR LINDENFELD: - that had bosentan
15 withdrawal?

16 DOCTOR KORBIN: No.

17 DOCTOR LINDENFELD: Okay.

18 Let me just move on for a minute. We've
19 seen that potentially bosentan increases the
20 metabolism of oral contraceptives, so that they might
21 be less effective. As I understand it, we don't know
22 for sure, but you are recommending additional

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1 contraception?

2 DOCTOR KORBIN: I would say two things, and
3 again, Doctor Rubin might want to comment I think.

4 Pregnancy is practically contraindicated
5 in patients with pulmonary arterial hypertension. It
6 is very dangerous to them, and it could be a lethal
7 event. So, we are recommending - and we don't
8 recommend using oral contraceptives because they might
9 lose the contraception, recommend double barrier, and
10 this is going to be discussed specifically with the
11 Agency and with the gynecologists in order to identify
12 the exact way how to make sure that they will not get
13 pregnant.

14 DOCTOR LINDENFELD: No, I understand it's
15 contraindicated, but, unfortunately, I think we've all
16 seen it happen. And, as I understand the drug then,
17 there could potentially be teratogenic effects prior
18 to the woman knowing she was pregnant.

19 DOCTOR KORBIN: Yes.

20 DOCTOR LINDENFELD: I mean, in fact, you
21 would expect that.

22 DOCTOR KORBIN: Yes, this could happen..

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1 Let me just add one more thing to what I
2 said before, also oral contraceptives are relatively
3 contraindicated in these patients because of the
4 tendency to thromboembolic phenomenon.

5 DOCTOR LINDENFELD: Right.

6 DOCTOR KORBIN: And, in fact, we have -
7 maybe Doctor Rubin would like to make just one comment
8 on this issue.

9 DOCTOR RUBIN: In general -

10 DOCTOR LINDENFELD: We can't hear you. We
11 need to get the microphone on up here.

12 DOCTOR RUBIN: In general, we discourage
13 our patients from using oral contraceptives for two
14 reasons, both of which are soft. One is the
15 thrombogenic risk that may be inherent, particularly,
16 in these patients, and the second is very limited data
17 that suggests that several patients who took oral
18 contraceptives with PPH had documented worsening of
19 their pulmonary hypertension condition, which improved
20 upon discontinuation of the drug, and recurred with
21 rechallenge. Those are old data from the U.K., but
22 they are out there.

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1 So, given alternatives, we try to use them
2 instead of oral contraceptives.

3 DOCTOR LINDENFELD: Okay.

4 But, am I correct in saying that even
5 before the first period was missed this is a
6 teratogenic drug?

7 DOCTOR KORBIN: Yes.

8 DOCTOR LINDENFELD: And, that's going to be
9 an important, I think, warning on this drug.

10 ACTING CHAIR BORER: Alan?

11 DOCTOR HIRSCH: Well, hopefully, you've
12 appreciated all the compliments for a really erudite
13 presentation. I just have two short questions, I
14 think, and I want to learn as much as I can about the
15 disease, and the receptors, and the antagonists before
16 we talk further.

17 One is, I don't know very much about the
18 natural history of what endothelium does in pulmonary
19 hypertension, either in animal models or in humans.
20 I am a little concerned about what happens to a
21 patient with a new diagnosis in the first month of
22 treatment.

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1 If I can make an analogy again to the
2 renal antigen system, is there an increase in
3 synthesis or circulation of endothelium during acute
4 exacerbations early in the disease that then abates
5 later? Whenever we have an opportunity to give
6 antagonists, I worry about what's happened to the
7 agonist, and that could provide us with an idea for
8 cautions in use, perhaps.

9 DOCTOR RUBIN: The experience so far with
10 endothelium in pulmonary hypertension, I would say are
11 three pieces. One, there is clear evidence of over
12 expression of endothelium in the lungs of patients
13 with pulmonary hypertension. It comes from all size
14 vessels, it is particularly impressive in the
15 plexiform, the most severe lesion.

16 Number two, circulating levels of
17 endothelium are increased, and they are quite markedly
18 increased, and the intrapulmonary clearance of
19 endothelium is impaired. So, there is an endothelium
20 clearance in the normal pulmonary circulation, that
21 clearance is impaired, suggesting alteration in
22 endothelial function in general.

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1 And, this is true, not only in primary
2 pulmonary hypertension but other forms, in particular,
3 the connective tissue disease.

4 Beyond that, the only other data that I'm
5 aware of regarding changes in endothelium levels over
6 time in patients with pulmonary hypertension is one
7 study that demonstrated that patients who had been on
8 Flolan for some period of time, and I believe it was
9 at least six months, perhaps a year, had improvement
10 in the intrapulmonary clearance of endothelium,
11 suggesting that there was some restoration of
12 endothelial function over time with that therapy.

13 DOCTOR HIRSCH: I appreciate that, and
14 actually the basic science and preclinical work in
15 endothelium is actually fairly well established, but
16 let me make it more clinically relevant.

17 If I'm a physician following a cohort of
18 patients with - if I'm you - with pulmonary
19 hypertension, and I were to draw serum levels in the
20 out patient setting, and there was an acute
21 decompensation and the patient comes in the hospital
22 by tripled levels, and is that a time period when I

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1 would be cautious in the use of this particular drug,
2 for example?

3 DOCTOR RUBIN: In a patient who had not
4 been on it previously, or -

5 DOCTOR HIRSCH: Or, who is on it, either
6 way actually, in other words, is the situation
7 entirely stable in terms of synthesis, secretion and
8 clearance of endothelium once the disease is
9 established?

10 DOCTOR RUBIN: I don't know the answer to
11 that, and to my knowledge that has not been looked at.

12 In patients over the course of time,
13 whether there are changes in their synthesis or
14 clearance over time, or as a function of their disease
15 state, other than with treatment with Flolan.

16 DOCTOR HIRSCH: Okay.

17 And then, sort of another sort of question
18 to relate the preclinical work to the hepatic
19 abnormalities you've demonstrated, other than
20 cholestatic mechanisms, again, are there hemodynamic
21 effects of endothelium in the hepatic circulation that
22 might affect, again, liver function, or does

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1 endothelium antagonism, per se, alter liver blood
2 flow, intrapatic blood flow? The liver is obviously
3 a target organ for drug effects, and the blood vessels
4 exist in the liyer.

5 DOCTOR CLOZEL: (Off mic at first) - to
6 cause decrease in - pressure in cases of elevated -
7 abnormally elevated - pressure. I don't think that it
8 could have relevance for the changes in liver enzymes
9 which we are seeing.

10 In cases of ischemia reperfusion, bosentan
11 was actually able to decrease - levels in animal
12 models.

13 DOCTOR HIRSCH: Thank you.

14 ACTING CHAIR BORER: Okay.

15 Just one more question, if I may - oh,
16 Doctor Anderson?

17 DOCTOR ANDERSON: I just have a quick
18 question. I believe you said that there were not
19 toxic metabolites. Do you know what the metabolites
20 are, and how did you arrive at that?

21 DOCTOR KORBIN: Again, I will ask Doctor
22 Clozel to respond to this.

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1 DOCTOR CLOZEL: We have studied bosentan
2 and its metabolites for the potential site toxicity on
3 human hepatocytes, and up to very high concentrations
4 the metabolites of bosentan did not cause any site
5 toxicity.

6 In addition, the metabolites of bosentan
7 suggest that there is no possibility for formation of
8 intermediaries for active metabolites.

9 DOCTOR ANDERSON: So, you haven't
10 identified the metabolites?

11 DOCTOR CLOZEL: We do, we have identified
12 the metabolites, and they are stable, rapidly formed,
13 and not cytotoxic.

14 DOCTOR ANDERSON: And, have you looked at
15 other drug interactions of the metabolites?

16 DOCTOR CLOZEL: Sorry?

17 DOCTOR ANDERSON: Possible drug
18 interactions of the metabolites. You don't understand
19 my question.

20 DOCTOR CLOZEL: No, I don't.

21 DOCTOR ANDERSON: Okay.

22 You've got metabolites, there's a

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1 possibility that the metabolites could interact with
2 other drugs, not the initial drug.

3 That's okay.

4 DOCTOR KORBIN: Maybe -

5 DOCTOR ANDERSON: Okay.

6 DOCTOR KORBIN: Maybe you want to answer
7 this question, Doctor -

8 DR. MONSUR: Just a short explanation of
9 the metabolites, as Doctor Clozel just explained, we
10 have identified three main metabolites in humans, and
11 all metabolites have been tested, measured, indeed,
12 drug interactions we have performed, and there's no
13 indication whatsoever that one metabolite peers out.
14 There are no differences, roughly speaking, in the
15 pattern for the concentration, time profile for the
16 parent compound bosentan in relation to that of the
17 three metabolites.

18 ACTING CHAIR BORER: One more question
19 before you go on to the liver.

20 Again, you must understand that my
21 question is not meant to be critical, because you set
22 up a study that's a good study, and you have a limited

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1 population form which to choose, as we heard
2 yesterday, 50,000 people in the world.

3 But, you did exclude patients with
4 congenital heart disease with presumed Eisenmenger
5 Syndrome, and you did exclude people, if I read the
6 booklet properly, with evidence of severe sclerosis,
7 systemic sclerosis, who might have had pulmonary
8 hypertension, and I can understand why you might do
9 that.

10 However, do you anticipate that if this
11 drug becomes available it will be given to those two
12 groups?

13 DOCTOR KORBIN: One of the things that we
14 are planning to do if the drug will become available
15 is, indeed, to test this drug in these specific
16 populations. We heard today about HIV patients, for
17 example, and the same thing would be for congenital
18 heart disease, and this is exactly where we want to go
19 if the drug will be approved and test this drug in
20 these patient populations.

21 ACTING CHAIR BORER: What would you suggest
22 that physicians should do now if they saw patients in

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1 these subgroups, and this drug became available?

2 DOCTOR KORBIN: We don't have any data in
3 these patient populations, so I think that we cannot
4 do anything before studying this drug in these patient
5 populations.

6 ACTING CHAIR BORER: JoAnn?

7 DOCTOR LINDENFELD: I'm sorry, we went
8 through this earlier about ketoconazole, but I just
9 would refer people to the pharmacologic review, the
10 FDA review, that suggests that concomitant
11 administration of bosentan and ketoconazole should be
12 contraindicated.

13 DOCTOR KORBIN: Contraindicated for?

14 DOCTOR LINDENFELD: Contraindicated.

15 DOCTOR KORBIN: I think that it is related
16 to a mistake, because they thought that there may be
17 a 30-fold increase with ketoconazole, the same as with
18 cyclosporin, which is not the case.

19 DOCTOR LINDENFELD: Okay.

20 DOCTOR KORBIN: There was only a twofold
21 increase and not 30-fold increase with ketoconazole,
22 so definitely they cannot be compared, these two

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1 drugs, and the twofold increase we believe is a modest
2 increase which will not put the patients at any risk.

3 DOCTOR LINDENFELD: All right. We'll have
4 to just make sure that that's correct.

5 ACTING CHAIR BORER: Doctor Brem?

6 DOCTOR BREM: I just had a quick question
7 about the pharmacokinetics of the drug. It's a
8 competitive inhibitor, is there anything known about
9 the effects of PH or, perhaps, other physical
10 circumstances which may affect the protein binding to
11 the receptor, endothelium receptors, that might in
12 turn determine efficacy of the drug?

13 DOCTOR KORBIN: Maybe I will ask our
14 pharmacokineticist will answer this question.

15 DR. MONSUR: I'm sorry, I have to correct
16 you, the drug is not an inhibitor of metabolism of
17 3A4, it's an inducer.

18 DOCTOR BREM: No, I said a competitive
19 inhibitor for the receptor, I'm sorry, it's a receptor
20 competitive inhibitor of the endothelium receptor, is
21 that not right?

22 DOCTOR KORBIN: Yes, that's correct.

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1 DOCTOR BREM: And, that receptor binding,
2 I assume it binds to the receptor and prevents the
3 true agonist from working, and that's how it
4 functions.

5 Is there anything in the physical
6 environment, for instance, change in local PH which
7 might affect that binding efficiency, or the
8 efficiency of the drug?

9 DOCTOR KORBIN: I don't think that we have
10 any data on these.

11 DOCTOR BREM: So, in other words, if there
12 were a local PH change that were instead of 74 it went
13 to 72, would that affect the receptor binding of the
14 antagonist to the receptor?

15 DOCTOR CLOZEL: I don't think that it's
16 specific, again, - the effect of PH on the affinity of
17 the - or bosentan work study, I can only answer in a
18 very indirect response that in animal models,
19 including models with certainly metabolic - and
20 ischemia, there was also efficacy of bosentan, and
21 that I don't think that we have any evidence that the
22 PH modified its efficacy.

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1 DOCTOR BREM: Thank you.

2 ACTING CHAIR BORER: Okay.

3 Why don't we go ahead to the presentation
4 about the liver, and then we'll have some questions
5 about the liver, and then your final risk benefit
6 presentation, and then we're going to take a break.

7 DOCTOR MADDREY: Thank you.

8 I've been asked to make a few comments
9 regarding the hepatotoxicity issues with this drug in
10 the context of what we've seen about hepatotoxicity
11 issues with other agents.

12 I thought it was worthwhile to start in
13 the first slides I have with the signals. The major
14 signals of drug-induced hepatotoxicity, starting from
15 the top of course, begin with acute liver failure that
16 leads to death, or a death equivalence, which is the
17 need for a liver transplantation procedure.

18 Just below that are those patients who
19 developed symptomatic liver disease with clinically-
20 apparent jaundice, those who have ascites,
21 encephalopathy and coagulopathy, all situations in
22 which it is obvious to the clinician that symptomatic

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1 liver disease is present.

2 The intermediate area is one in which we
3 work most often, and this relates to the frequency
4 with which an individual chemical agent will cause
5 aminotransferase elevations in a variety of
6 situations.

7 Most hepatologists agree that anything at
8 the eight times the upper limit of normal or higher is
9 an indication of potentially significant
10 hepatotoxicity. At a range of five, there is a zone
11 of safety. Many will say that the safest way to
12 approach therapeutic drugs is to consider removal of
13 the drug at five times the upper limit of normal,
14 unless there are other circumstances, such as a life-
15 saving nature of a drug that requires one to be used
16 beyond that.

17 Many times, we use the three times upper
18 limit of normal as rather much our threshold to
19 compare drugs from many classes of use.

20 Minor elevations are common in the
21 population in general, and, of course, slight
22 elevations of aminotransferases are found particularly

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1 in patients who take drugs, those who are obese, and
2 are also found in situations of non-specific findings,
3 a whole variety of situations that we find these days.

4 The, relevance of the elevated
5 aminotransferases, as I mentioned, is in the eye of a
6 risk benefit type of assessment. There's quite an
7 inexact correlation between slight elevations and the
8 presence of injury. It's important to note the
9 associated signs and symptoms. It's important to use
10 at least the two markers noted here, the greater than
11 three times the upper limit of normal, which is a
12 threshold that should lead a clinician to at least in
13 an asymptomatic patient recheck the aminotransferase
14 levels and determine whether there is a progressive
15 elevation, and a five X should trigger considerably
16 heightened awareness.

17 One of the important points to know is
18 that, as we gain experience with an individual drug it
19 gathers a signature. For example, phenitoin will
20 cause most of its significant liver injury within one
21 month of starting the drug. It's signature is early
22 onset, patients who have taken that drug for a period

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1 of time, beyond a month, will rarely have significant
2 problems develop. Another signature is with
3 isonizide, patients taking isonizide have a 10 to 20
4 percent chance, and in some series even more, of
5 elevating the aminotransferases within the first few
6 weeks to months after taking the drug. In many of
7 those patients, this is of no consequence and will
8 self-correct with continued administration.

9 In other drugs, an elevated
10 aminotransferase has a different significance, and
11 only by learning the signature of the drug can we make
12 an appropriate assessment.

13 You heard mention of the Zimmerman rule,
14 Zimmerman law. Many of us who work with drugs revere
15 the observations of the late Doctor Hy Zimmerman. He
16 worked predominantly on this in relation to drugs that
17 were pure hepatocellular drugs, drugs that present
18 with elevated aminotransferases and not those who had
19 elevations in the alkaline phosphotase. As we've
20 already heard, bosentan does interfere with the bile
21 salt excretory pump. This can cause an elevation of
22 alkaline phosphotase and bile acids in some patients.

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1 However, I think all of us agree that a
2 patient who has a drug-induced hepatotoxicity with
3 evidence of significant hepatocellular injury, going
4 beyond three times the upper limit of normal, and
5 clinical jaundice, that is a serum bilirubin in the
6 range of 3 mg/dl or greater, is at increased risk
7 compared to those individuals who have acute viral
8 hepatitis and meet the same standards.

9 I mentioned three drugs here to make this
10 point, all three of which Doctor Zimmerman studied,
11 and I had the opportunity to participate in two of the
12 three with him. In isonizide, those patients who met
13 this criteria, particularly, in those who were older
14 than 50 years at the time of receiving the isonizide,
15 there was roughly a 10 percent mortality if you had
16 the so-called Zimmerman rule criteria met.
17 Methyldopa, another drug that is familiar to many in
18 this audience, will do the same thing if the criteria
19 are met. This does not mean that methyldopa or
20 isonizide is a particularly dangerous drug, because
21 the vast majority of patients who take these agents
22 never achieve these levels.

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1 Tienillic acid was a drug that taught us
2 all many lessons. This was a uricsuric diuretic,
3 short lived, removed quite quickly a number of years
4 ago, and in it, when we had an opportunity to study
5 the entire database from the Food and Drug
6 Administration and the manufacturer those patients who
7 went beyond the three times three times rule had
8 roughly a 10 percent mortality.

9 Bosentan we know a lot about, and Doctor
10 Korbin has told us a good deal of it. Just to try to
11 put it in a bit of perspective, this drug does cause
12 hepatotoxicity. It's predominantly hepatocellular,
13 but it has a mixed component. The fact that it has a
14 mixed component means that the Zimmerman rule doesn't
15 apply quite as fully, because part of the elevation in
16 the bilirubin may be from the less dangerous
17 canalicular component.

18 There was, however, a higher incidence of
19 ALT than we see with many other agents that have come
20 before and been approved by the Agency, roughly, 10 to
21 12 percent of patients taking this drug will show an
22 elevation beyond the 3X threshold.

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1 The signature of the drug is quite a clear
2 one. The onsets occur almost exclusively in the first
3 16 weeks, telling us that we must pay attention to
4 this drug early in the course of its use. Many of the
5 elevations did self-correct from various levels while
6 the drug continued, suggesting there are metabolic
7 adjustments possible, maybe even more importance all
8 of the elevations that were seen returned to normal
9 and there has been to this date no case of acute liver
10 failure, and, furthermore, no case of any evidence of
11 a patient having received this drug showing evidence
12 of residual liver injury of any type.

13 I have worked with this drug now, and with
14 a panel of hepatologists advising the company, and
15 think that the risk reduction plan that would require
16 biochemical tests pretreatment monthly for six months
17 and quarterly thereafter, with a discontinuation at
18 five times the upper limit of normal, or in any
19 patient who developed clinical jaundice or symptoms of
20 liver disease would offer us a degree of safety.

21 Since we've not seen a case of acute
22 hepatic failure, we can hardly give a number.

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1 However, if we took the worst case, as Doctor Korbin
2 outlined, three out of 1,500 have shown and met the
3 minimum criteria of the Zimmerman rule, extrapolate
4 that out, assume the 10 percent, I would say the
5 safety of this drug as far as causing serious liver
6 disease is somewhat better than one in 5,000.

7 Thank you very much.

8 ACTING CHAIR BORER: Thank you.

9 Doctor Maddrey, if you would stay up
10 there, there will be several questions I'm sure. Just
11 tell me, that was 10 percent mortality over what
12 period of time?

13 DOCTOR MADDREY: That's acute mortality,
14 when patients develop acute liver failure that would
15 be - that would be a situation that would resolve
16 itself in a month or six weeks at the outside.

17 ACTING CHAIR BORER: I see.

18 DOCTOR MADDREY: That's what was called in
19 the more common parlance, - hepatic failure.

20 ACTING CHAIR BORER: Okay, thank you.

21 Steve?

22 DOCTOR NISSEN: Yeah, and I think this is

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1 a question that I think any of you from the group can
2 answer for me.

3 What we're at now is the crux of our
4 decision, because I think it's pretty clear that
5 efficacy was shown, and now the question is, what is
6 the real risk?

7 I need to understand how many patient
8 years of exposure there have been to this agent. I
9 know there are 1,522 patients in the database, but I'd
10 like to know how many patient years of exposure there
11 are, and once I have that answer I'm going to offer a
12 second question.

13 DOCTOR KORBIN: I think that this is where
14 we can see the answer to your question, this is the
15 patient years for pulmonary arterial hypertension,
16 this is for patients in the rich 1 trial with its open
17 label, and this is for the ENABLE. This does not
18 include the other parts in hypertension, sub -
19 hemorrhage, where there was only short-term treatment
20 duration. So, this is what we know today about the
21 patient years of exposure when we take altogether the
22 exposure to bosentan.

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1 DOCTOR NISSEN: All right.

2 Now, let's just roughly say about 2,000 or
3 a little bit more patient years, is that in the
4 ballpark?

5 DOCTOR KORBIN: Yes, I would say, although
6 in ENABLE you have to take into consideration that
7 it's about half, because half of the patients are on
8 bosentan.

9 DOCTOR NISSEN: Yes, okay.

10 So, let's say, let's for the purposes of
11 discussion say 2,000 patient years. Now, the question
12 is, suppose the incidence of hepatic failure and death
13 had an incidence of one in a 1,000 with this drug, for
14 example, would we be - to what degree of confidence
15 can we rule out that the rate is greater than one in
16 a 1,000?

17 And, if you do the calculations, and I
18 kind of did this in my room last night, basically, the
19 amount of exposure that we have, would you agree, is
20 insufficient to rule out a rate of hepatic lethality
21 up to about one in a 1,000?

22 DOCTOR KORBIN: I think that it is very

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1 difficult to assess the risk. The best that we can is
2 based on the Zimmerman criteria. And again, based on
3 this, on a theoretical basis, one can assume that in
4 the worst case it will be one in 5,000.

5 DOCTOR NISSEN: No, but I'm not interested
6 in the theoretical issues, I'm interested in what does
7 the data actually tell us, what degree of security do
8 we have based upon the amount of exposure?

9 And, as I calculate it, something like,
10 and Tom Fleming can probably do this a lot better than
11 I could, but I'm going to suggest that what we know is
12 that with no cases of liver failure, and given the
13 amount of exposure that's occurred, we cannot rule out
14 the possibility of death due to hepatic failure from
15 this drug up to about one in 700 or 800.

16 Tom, could you help me out here a little
17 bit? Am I in the ballpark?

18 DOCTOR FLEMING: Yes. If we assume the
19 rate was one in 1,000, and we observed 1,500 people,
20 then we would have had a 78 percent chance of seeing
21 at least one case of - hepatic failure. So, if you
22 see none, if you don't consider a 78 percent power

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1 adequate, you want a 95 percent power.

2 DOCTOR NISSEN: I do. I do.

3 DOCTOR FLEMING: Then, it's essentially one
4 in 1,000. So, essentially, if the rates were - excuse
5 me, it would be more on the order of two in 1,000, is
6 what we can rule out, because if there were a two in
7 1,000 true rate then we would have had a 95 percent
8 chance of seeing at least one case of - hepatic
9 failure in 1,500 people. So, we are more in the area
10 of being able to say it's unlikely that the rate is
11 higher than one in 500.

12 DOCTOR NISSEN: Right, and, you know, I
13 don't think - I mean, just my own viewpoint here is,
14 I don't think that the theoretical extrapolation from
15 experience with other drugs is going to help us very
16 much here. You know, we've had some rather unusual
17 experiences with drugs like Troglidizone, which was
18 removed from the market for hepatotoxicity, where, you
19 know, obviously, there was a pretty good safety
20 database, but it wasn't sufficient to predict what was
21 going to happen.

22 DOCTOR KORBIN: Maybe we can answer with -

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1 DOCTOR TEMPLE: Can I comment on that?

2 Actually, if you run numbers, of course,
3 you are making a lot of assumptions, Troglidizone
4 follows Hy's rule, too, in the original database there
5 were two or three people who had elevated bilirubin
6 along with their transaminase elevations, which were
7 much more frequent, which you might think corresponds
8 to a rate of about one in 3,000 of those - one in
9 1,000 of those, and, therefore, a rate of, perhaps,
10 one in 10,000 people with serious injury.

11 There are various estimates of how many
12 serious injuries there were from one in 50,000 to one
13 in 2,000, but my guess is that one in 10,000 is in the
14 ballpark.

15 So far, you know, you never know about the
16 drug that's different from all the past experience
17 until you see it, for the drugs that have been
18 hepatotoxic, whether it's isonizide, ipronizide,
19 things like that, the roughly - the idea that you can
20 get some idea of what serious injury is going to be
21 from looking at people with less serious injury has
22 held up amazingly well, considering how few

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1 experiences it's actually based on.

2 So, you are literally correct, you can't
3 rule out events that were unseen at a rate, you know,
4 roughly corresponding to the rule of three, that's
5 always true. That's true for every drug we ever see.
6 If we have a database of 3,000 people, that means
7 we've ruled out a rate of .1 percent mortality for
8 something we never saw.

9 But, for what it's worth, and we've looked
10 fairly much at this, as has Will, for hepatotoxins
11 that are hepatocellular injury causing drugs, which
12 are the ones we worry about most, about 10 percent of
13 the people who get a bilirubin elevation accompanying
14 their transaminase has held up remarkably well over
15 time. That doesn't mean it always will.

16 DOCTOR KORBIN: Maybe we can - Doctor
17 Maddrey, would you like to add to this?

18 DOCTOR MADDREY: Well, I can't add to that,
19 of course, I have extensive experience with the
20 Troglidizone story, a database that was much larger,
21 but did have some signals.

22 I must say that it would be remarkable if

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1 we could, for this indication, come up with the types
2 of numbers that would give us security at the one in
3 10,000 range.

4 I think one difference between the
5 approach to that drug and this one, and from advice of
6 a number to this company, this drug will go in with a
7 strong set of recommendations about how it should be
8 followed and managed, and a number of safeguards put
9 in place that were not put in place with a number of
10 other agents that have caused hepatotoxicity in the
11 last few years.

12 I could mention tacrin, a drug that had
13 25 percent of patients who received that drug, had a
14 greater than three times elevation, but the Agency
15 thought in its wisdom that that was first drug in for
16 Alzheimer's, it looked like it might have some
17 benefit, we did extraordinarily stringent requirements
18 for testing, and to my knowledge we've not had a
19 single death that I'm sure of. There's one in the
20 literature, and one more I've heard of, but that drug
21 went in with a monitoring schedule that was really
22 quite severe. I thought, if anything, over severe,

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1 but because the patients needed additional protection,
2 so we were able to handle a drug like that with no
3 clinical hepatotoxicity thus far.

4 DOCTOR NISSEN: That's, of course, because
5 we saw no bilirubin elevations.

6 Please understand that I also recognize
7 here that when the disease one is treating is a
8 disease with a high lethality that some safety
9 tolerance can be very different, but I wanted to get
10 a handle on what the real risks are.

11 ACTING CHAIR BORER: Ray?

12 DOCTOR LIPICKY: I guess it's two things I
13 want to say. We are lucky here, in that there were
14 other indications studied by the sponsor also, so that
15 their overall is a larger exposure, but had we
16 limited, had this only been a database limited to
17 pulmonary hypertension we wouldn't be talking about
18 ruling out things that were occurring at one in 300,
19 or one in 500, okay?

20 Now, with that said, also understand that
21 we, as an Agency, said making people feel better
22 without having any morbidity or mortality data that

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1 convinced us that there was clinical efficacy for the
2 drug would be enough to bring it to you for a
3 decision.

4 Now, that's a fairly big statement, and
5 you may be able to criticize that, because, in fact,
6 we have seen yesterday and today that there is no
7 evidence that in this disease that is fatal, and so
8 terrible, that any of the drugs alter the fatality or
9 the terribleness. The only thing we have asked the
10 sponsors to provide is feeling better, and that's it.
11 We thought that was enough, but you might comment on
12 that when, in fact, you are being asked to make a
13 decision about approving the drug without being able
14 to rule out things that are occurring fatally at an
15 incidence of one in 300.

16 ACTING CHAIR BORER: Ray, you know all of
17 us better than to think that any of us would be
18 critical of anything you had ever done.

19 Now, do we have anymore liver-related
20 questions? Bob?

21 DOCTOR TEMPLE: Well, I wanted to provide
22 at least some of our historical reassurance about

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1 using Hy's law. I also want to point out that we have
2 very little reason to believe that liver monitoring
3 prevents bad news.

4 Now, I don't know whether it might in this
5 case, where the ride seems to be, perhaps, more
6 leisurely, but certainly for major hepatotoxins, like
7 troglidizone, you can go from no problem to major
8 problems in a very short time in at least some of the
9 patients. And, you can't be really confident, I think
10 the program that's planned seems reasonable enough,
11 but you can't be for sure, you can't know for sure
12 that that's going to prevent trouble as a general
13 matter. Maybe for this kind of injury with some
14 biocomponent you could, but as a general matter we
15 don't know the answer to that, even though we
16 recommend it lots of times.

17 DOCTOR MADDREY: I would like to comment on
18 that. Doctor Temple and I agree entirely, most
19 monitoring is not followed, and very little of
20 monitoring has ever been proven to work.

21 However, these are patients more likely to
22 be monitored, as maybe the Alzheimers were, because

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1 these are patients who are under regular medical care,
2 and I think with the - I was for monitoring here, and
3 I'm often not for monitoring because I think it's a
4 big waste of time and money, but I think that
5 monitoring will ensure awareness of these liver issues
6 in this situation, and awareness might be enough to
7 keep us to a very acceptable hepatotoxicity cost.

8 ACTING CHAIR BORER: JoAnn?

9 DOCTOR LINDENFELD: Just a quick - Doctor
10 Maffrey, just a quick question for you, utilizing your
11 expertise here. What recommendations would you make
12 of the use of this drug with other drugs that are
13 excreted in a biliary fashion and other drugs that are
14 hepatotoxins, and do we have a reasonable list of
15 those drugs to provide to physicians?

16 DOCTOR MADDREY: Well, I certainly wouldn't
17 use it with glibenclamide, which is shown to affect
18 this bile salt excretory pump. It's a pump that's
19 only been identified for a while. There are a list of
20 drugs that we're learning that are affected.

21 DOCTOR LINDENFELD: So, we don't know all
22 of those yet.

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1 DOCTOR MADDREY: We really don't know all,
2 and we don't know how much each one would be affected
3 on this pump.

4 Actually, I think many patients receiving
5 this drug will have some slight elevation of serum
6 bile acid, which should be of no clinical consequence,
7 so I can't answer that. I think only experience will
8 tell us that.

9 ACTING CHAIR BORER: Doctor Brem?

10 DOCTOR BREM: Is there anything known about
11 common over-the-counter agents in interacting with
12 this particular drug, specifically, acetaminophen,
13 which is liver excreted, and alcohol, which,
14 unfortunately or fortunately, is ubiquitous, and I
15 suspect even patients with pulmonary hypertension may
16 have a glass of wine from time to time.

17 DOCTOR MADDREY: Yes, there's no evidence
18 in the acetaminophen or alcohol metabolism which
19 happen to have some commonalities through the P450
20 2E1. There's no evidence that either of these
21 pathways affect the bile salt pump, to my knowledge.

22 ACTING CHAIR BORER: Okay.

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1 We'll take a break now, and then have the
2 summary and any other questions afterwards, because we
3 are not going to have the opportunity to take a lunch
4 break.

5 It's 11:05 now, we'll start again at
6 11:35.

7 (Whereupon, at 11:05 a.m., a recess until
8 11:37 a.m.)

9 ACTING CHAIR BORER: Doctor Rubin, you are
10 going to do the risk benefit assessment. Just before
11 you start, are there any burning issues that anyone
12 wants to raise that we can't raise in the context of
13 the discussion? I take that as a no.

14 Doctor Rubin, go ahead.

15 DOCTOR RUBIN: Thank you.

16 I'd just like to conclude this
17 presentation with a very brief overall overview of
18 risk assessment of bosentan for pulmonary artery
19 hypertension.

20 The committee heard this morning, I think,
21 a very personal and very eloquent description of the
22 impact of pulmonary artery hypertension on patients.

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1 You've also heard over the last few days, and again
2 today, that the treatment options for this disease are
3 really quite limited, and quite complex. Clearly, new
4 treatments that are effective are needed for our
5 patients.

6 The benefits of bosentan treatment have
7 been presented here today, and let me just summarize
8 them. Treatment with oral bosentan is associated with
9 improvement in the six-minute walk test, improvement
10 in dyspnea score during exercise, improvement in WHO
11 functional class, delay in time to clinical worsening,
12 and at least in the early study in which hemodynamic
13 parameters were measured substantial improvement in
14 hemodynamic parameters. These are all clinically
15 meaningful, clinically relevant improvements in
16 patients' symptoms for patients who suffer from this
17 disease.

18 Furthermore, there was a maintenance of
19 the treatment effect with no evidence for tolerance,
20 at least with the patients that we've been able to
21 study so far on long-term open label therapy, some
22 patients for periods extending beyond one year.

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1 There are also, however, risks that are
2 associated with bosentan treatment for a PAH.
3 Treatment with bosentan is associated with decreases
4 in hemoglobin concentration, an increased incidence of
5 elevated liver aminotransferases.

6 With regard to the most significant of
7 these, the elevated liver transferases, this has been
8 characterized quite well, and as Doctor Maddrey
9 discussed with you the abnormality has a signature
10 that has been fairly well characterized and
11 identified.

12 The risks have, to some extent, been
13 quantified with regard to incidence, at least per the
14 discussion earlier, and the degree of severity. Most
15 importantly, at least at this point, there's no
16 patient who has suffered irreversible liver disease or
17 progressed on to liver failure.

18 And, as has also been discussed, the liver
19 aminotransferases can be monitored within the current
20 pulmonary hypertension treatment paradigm, and I think
21 this is a very important point. The vast majority of
22 patients with fairly severe pulmonary hypertension are

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1 cared by a relatively small cadre of physicians who
2 specialize in the management of this disease.

3 And, as our treatment algorithm becomes
4 more complicated, more complex, it will be even more
5 important for us to be involved in the management of
6 these patients to determine which treatment option is
7 best suited for that patient.

8 As part of our routine treatment paradigm,
9 we monitor blood testing for INR, blood chemistries,
10 regularly. This can easily be incorporated within
11 that paradigm, and because of that, and because the
12 patients will be cared for, to a large extent, by
13 physicians with expertise and with knowledge of this,
14 we at least will have the opportunity to monitor it
15 and at least the opportunity to intervene early if
16 abnormalities in liver function do develop.

17 So, let me finish by saying that I believe
18 you've seen today that treatment with bosentan
19 produces clinically meaningful benefits that
20 substantially outweigh its characterized risks, and
21 that oral bosentan fulfills an unmet medical need in
22 patients with PAH.

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1 Let me just finish, if I can, by
2 addressing very briefly a point that I think Doctor
3 Temple raised previously, with regard to the low dose,
4 the 62.5 mg dose, from a very practical standpoint.

5 I think that the 125 mg dose was chosen to
6 try to achieve the best result with the drug. I think
7 there may be a signal that a lower dose in some
8 patients, or maybe more patients, could be beneficial.
9 I think it may be reasonable to try that dose in
10 patients, and if they are achieving a substantial
11 benefit, and the clinical assessment is it's a
12 substantial benefit, to stay at that dose. If they
13 are not, to go up to what we have shown I think is
14 clearly an effective dose.

15 Thank you.

16 ACTING CHAIR BORER: Thank you.

17 Are there any final questions for Doctor
18 Rubin, or can we handle those?

19 Bob?

20 DOCTOR TEMPLE: I'm not sure who my
21 question is for.

22 Is there a treatment protocol going on

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1 now? This is in response to Mr. Delaney's question,
2 is there currently a compassionate program or
3 something like that, because I couldn't tell what
4 program people with AIDS were being excluded from.

5 DOCTOR RUBIN: Yes, there is an ongoing
6 open label compassionate use program. It was started
7 relatively recently, within the last month or so, at
8 the centers that were involved in the clinical trial.

9 The entry criteria for the open label
10 protocol parallels the entry criteria in a clinical
11 trial. So, patients that were excluded, which included
12 HIV patients, Eisenmenger Syndrome patients, are not
13 being included in the open label trial. We have no
14 data on those. But, the intent was, based on the data
15 that you've seen to avail patients who meet the
16 indicated criteria, to avail those patients as soon as
17 possible of this therapy.

18 ACTING CHAIR BORER: Steve?

19 DOCTOR NISSEN: I want to challenge you on
20 one of the statements you made, and that is that these
21 patients are cared for by a fairly small and narrow
22 group of physicians. I think that's been traditionally

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1 true, when the therapy was Flolan, but what we have
2 now is a twice a day oral medication, and I really -
3 I'm concerned a bit that what's going to happen is,
4 people who are not among the cognizant are going to
5 start to treat these patients, that the expertise that
6 has existed up until this date is going to now diffuse
7 a bit, and I'm worried about off label use, I'm
8 worried about misuse, I'm worried about people who
9 push the dose inappropriately, and I really would like
10 your from-the-heart assessment of that.

11 DOCTOR RUBIN: It's a valid point, and
12 there is the risk that we could be the victims of our
13 own successes, that we could put ourselves, to some
14 extent, out of business as pulmonary hypertension
15 experts.

16 However, I think that my experience has
17 been that physicians are quite willing to refer their
18 patients for assistance in management, and even if the
19 management is less complex and less time and labor
20 intensive as Flolan, because the algorithm is getting
21 complicated, it's getting complicated by virtue of
22 your actions yesterday and today, transplantation is

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1 something that we haven't really discussed, but it is
2 an option for many of these patients. The selection
3 of patients, the timing of patients for transplant on
4 therapy is not something that we leave to the judgment
5 of the practicing pulmonologist, cardiologist,
6 internist in the community.

7 So, we follow those patients within our
8 own system and make the judgments about what treatment
9 option, medical or surgical, while clearly there may
10 be some risk of inappropriate use, inappropriate
11 dosing, and care of those patients, and the easier the
12 treatment the greater the risk.

13 I think that the more treatments that are
14 available the greater the likelihood that our
15 expertise will be sought to help choose among those.

16 ACTING CHAIR BORER: Doctor Rubin, what
17 would you say, I mean we have no data, of course, but
18 just your opinion, what if somebody - what if this
19 agent is approved and somebody chooses to prescribe a
20 half a pill, half of a 62.5 twice a day, and tells
21 someone see if you feel better with that, what would
22 you think about that?

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1 DOCTOR RUBIN: You know, I'm happy to speak
2 from opinion without data, it's a luxury. You know,
3 I can't exclude the possibility that, you know, even
4 less than that is an effective dose. My own sense,
5 and my own experience, has been that the few patients
6 that we had, that I saw, that had been down titrated
7 to 62.5 as part of the change to the open label, or
8 the change over to the second period, those patients
9 did not do as well on the 62.5 compared to the higher
10 dose.

11 Now, that's my own very limited
12 observation. Nevertheless, I think if a patient up
13 titrated had a phenomenal clinical response to 62.5,
14 I'd probably keep him there for a while.

15 ACTING CHAIR BORER: Alan?

16 DOCTOR HIRSCH: We're all pursuing sort of
17 the same line before we opine more specifically about
18 the questions.

19 In the open label program, what are the
20 instructions that the physicians are to follow? Are
21 they specifically told now to take the patient from
22 62.5 and up titrate, or are they allowed to do what

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1 they see fit? What are the instructions?

2 DOCTOR KORBIN: The instructions at the
3 moment is that they treat the patient with 62.5 mg,
4 however, if there is symptoms developed because of the
5 start of this dose they are instructed to increase the
6 dose if they find it appropriate, and if the patient
7 is doing well they go to 125 mg twice a day.

8 We have seen in our long-term program that
9 in some patients where after one and a one a half
10 years there were some more symptoms, then the
11 investigators were allowed to even to 250 mg twice a
12 day, and there was an improvement in these patients.

13 So, in fact, it's in the hands of the
14 investigators now, if they want to treat it with 62.5,
15 125 or even 250 during the open label trial, but most
16 patients are on 125 twice a day.

17 DOCTOR HIRSCH: The more words I hear the
18 more difficult it is for me to focus on the answer.
19 It's my problem.

20 Are they encouraged to titrate up?

21 DOCTOR KORBIN: Yes.

22 DOCTOR HIRSCH: They are encouraged to

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1 titrate up.

2 DOCTOR KORBIN: Yes.

3 DOCTOR HIRSCH: Then I guess the question
4 is, based on the evidence and the discussion today,
5 would you ask physicians in the future to titrate up
6 or would you ask them to maintain at a lower dose, the
7 62.5?

8 DOCTOR KORBIN: I think that the best
9 answer was given by Doctor Rubin, if they start on
10 62.5 and there is a tremendous effect maybe they can
11 stay on it. If not, they might go to a higher dose,
12 and then get maybe a better effect.

13 DOCTOR RUBIN: I'd be very comfortable with
14 doing that, although it's not specified in the open
15 label protocol, I'd be very comfortable if the patient
16 is doing well on 62.5, not pushing up.

17 DOCTOR HIRSCH: I guess then I'll just
18 offer just an opinion for the record, following Doctor
19 Nissen's comment, which is, we were sort of talking at
20 the break about when does an orphan disease no longer
21 become an orphan disease, is it when there's one, or
22 two, or three, or five different medications? And, I

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1 might opine that it becomes no longer an orphan
2 disease when there's an orally active compound that's
3 perceived to be effective, that could be in the hands
4 of many physicians.

5 And so, I would caution us to not assume
6 that your expertise will be called upon. I can easily
7 imagine in our practice environment that the
8 availability of an orally active agent will permit the
9 diagnosis to be established more frequently, again for
10 the population for which the foundation is advocating
11 to be exposed to a drug which will inevitably have
12 some unknown risk of adverse effects.

13 DOCTOR KORBIN: If I could just comment one
14 word a bit. I think that the indication orphan
15 disease is not related to the number of medications
16 but to the number of patients.

17 DOCTOR HIRSCH: Oh, it's just a perception,
18 I understand that, there is a legal definition, but
19 how we act as physicians is beyond that, it's based on
20 perception.

21 DOCTOR TEMPLE: It's orphan forever. It
22 doesn't matter how many treatments there are, but that

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1 may not be the definition anybody really cares about,
2 that's the one that applies for purposes of tax breaks
3 and things like that.

4 ACTING CHAIR BORER: Okay.

5 DOCTOR TEMPLE: Can I ask one follow up
6 question?

7 The symptomatic improvement is the major
8 thing that you went for, and the major thing, as Ray
9 pointed out, you were encouraged to go for, but you
10 also have data from the combined data set that
11 suggests that some of the more important consequences
12 are also benefitted. You have no information about
13 62.5 on those effects at all. So, I mean, I must say
14 I'm not sure what I think, but that seems like an
15 important consideration also.

16 DOCTOR RUBIN: I think that's a very
17 valuable point.

18 ACTING CHAIR BORER: Yes, that's important,
19 and I'm sure we'll discuss it in giving you our best
20 advice.

21 Okay. I think that - thank you very much,
22 Doctor Rubin, and Doctor Korbin, for a really lucid

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1 presentation.

2 We'll go on to the committee
3 consideration, and again, with a summary statement by
4 the committee reviewer, Doctor Lindenfeld.

5 DOCTOR LINDENFELD: Let me just briefly
6 summarize what I think we've heard today.

7 We have heard very clearly, yesterday and
8 today, that we are dealing today with a very serious
9 illness that has a significant morbidity and
10 mortality, for which there are few treatments, and the
11 treatments are certainly not ideal, difficult, involve
12 a lot of morbidity on their own.

13 Today, we have a drug that I think we
14 would all agree is clearly effective in improving
15 symptoms and exercise capacity, and the decision
16 depends on how we feel about safety issues here. It's
17 a drug that has definite safety issues. We have liver
18 toxicity, which is probably the greatest safety issue.
19 We seem to be relatively comforted in that it's not a
20 high incidence, but there will be, I think, some liver
21 toxicity, and that in my view secondarily we have some
22 major pharmacokinetic interactions.

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1 I think that we haven't quite explored all
2 of those yet. I believe that cyclosporin is said to
3 be contraindicated. I would disagree with your
4 conclusions about ketoconazole, in fact, you have no
5 acute data with ketoconazole, you only have chronic
6 data, and if that's all we had with cyclosporin we
7 would have made the same conclusion about cyclosporin.
8 And, I think we are going to have to say that probably
9 all 3A4 inhibitors should be contraindicated, and
10 those include ratinovir, I think, and erythromycin.
11 That will be one important point.

12 Then we have some substantial protein
13 binding problems, which I think are probably not
14 important, but in some patients may be important, less
15 so, though, than what will we do about combining these
16 drugs with other potential hepatotoxins, and then
17 drugs excreted in the bile which we've heard are now
18 incompletely characterized. So that, we are going to
19 hear more about the potential toxicities of this drug.

20 It also has teratogenic effects.
21 Unfortunately, women will see those effects before
22 they know they are pregnant. On the other hand, this

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1 is a population of patients that we monitor already
2 for that, and pregnancy is uncommon.

3 And then in addition, there are effects on
4 anemia and probably some white cell effects, those do
5 not appear to be severe.

6 So, again, the balance here is a clearly
7 effective drug and a serious illness with some
8 substantial safety issues.

9 ACTING CHAIR BORER: Okay, thank you,
10 JoAnn.

11 Why don't we begin then with the
12 structured response here. The two principal
13 effectiveness studies assessed six minute walking
14 distance and demonstrated effects favoring bosentan
15 with p-values noted here.

16 The prospective analysis plan included
17 rules for handling the data from subjects who withdrew
18 prior to the final assessment, how does the handling
19 of early withdrawal affect the results? Tom, do you
20 want to make a comment about that?

21 DOCTOR FLEMING: Yes.

22 Briefly, the withdrawal rates in the trial

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1 were not notably high, and the majority of these were
2 worsening conditions or death. The analysis used a
3 worst outcome, and that was very appropriate. There
4 were very few AEs, and their handling in the analysis
5 has minimal impact.

6 So, the appropriate analyses were done.

7 ACTING CHAIR BORER: Okay.

8 So, the six-minute walk was the primary
9 endpoint in these studies, but there were other
10 measures of clinical benefit. I guess 1.1.2 refers
11 not only to bosentan, but sort of the more generic
12 issue that we grappled with yesterday to some extent,
13 what's the role of secondary endpoints where the
14 treatments are clearly distinguishable on the primary
15 endpoint?

16 Paul, do you want to give your opinion
17 first?

18 DOCTOR ARMSTRONG: To the extent that the
19 secondary endpoints are supportive and, perhaps, more
20 easily discernible in clinical practice, and
21 reflecting on the dose response issues that are
22 unresolved, I think I, as a clinician, if this were

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1 approved tomorrow, would utilize those secondary
2 endpoints to establish in my mind the minimally
3 effective dose to avoid the potential for toxicity.

4 ACTING CHAIR BORER: Does anybody want to
5 add anything to that?

6 DOCTOR FLEMING: Just briefly, certainly as
7 we've discussed a number of times there ought to be
8 primary focus on the primary endpoint, but in any
9 trial, whether the primary endpoint is compelling
10 positive or not, there is, obviously, a need for a
11 global assessment of all relevant data, and looking at
12 benefit to risk.

13 In a study such as this, where there is a
14 very strong effect on the primary endpoint, unless
15 there was something strikingly unfavorable on
16 secondary measures, it wouldn't have a great
17 influence. I would note that there are, in this case,
18 secondary endpoints that are especially compelling.
19 Bob Temple was referring to those a bit earlier, and
20 the favorable results on those secondary endpoints
21 become even very significantly further strengthening
22 the efficacy case.

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1 ACTING CHAIR BORER: Okay.

2 Steve?

3 DOCTOR NISSEN: You know it's interesting,
4 we are fortunate here in that everything went in the
5 right direction, but we could have been confronted
6 with a more difficult problem, which is that
7 improvement in the primary endpoint, with let's say a
8 trend toward worsening of those secondary endpoints,
9 and just like we said yesterday, we don't want to be
10 a slave to the p-value, we probably also shouldn't be
11 a slave to the primary endpoint.

12 And, just as a word of kind of comment for
13 anybody, you know, doing development of new drugs, I
14 think we probably could squeak by if the secondary
15 endpoints didn't make statistical significance and the
16 primary endpoint was very strong, but I think we may
17 some time very soon be confronted with situations
18 where the secondary efficacy parameters are kind of
19 trending in the wrong direction. And, I think that we
20 don't want to put ourselves in the position where the
21 only thing that counts for approving an agent is
22 whether you made your primary endpoint or not, because

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1 I think that's shortsighted.

2 ACTING CHAIR BORER: Okay.

3 Ray, have you heard all the advice on that
4 that you need? .

5 DOCTOR LIPICKY: Yes.

6 ACTING CHAIR BORER: Okay.

7 1.2.2, JoAnn, why don't you just go
8 through all these. If bosentan were to be approved
9 what should the label say are the effects of bosentan
10 on the following parameters, just go through the whole
11 list, and if anybody has anything to add they'll do it
12 at the end.

13 DOCTOR LINDENFELD: I think we could say we
14 don't know that there's no effect on mortality that we
15 are aware of. It does improve disease progression and
16 need for other drugs, functional class, Borg dyspnea
17 index, and hemodynamics.

18 ACTING CHAIR BORER: Okay.

19 The hospitalizations?

20 DOCTOR LINDENFELD: I can't remember if the
21 hospitalizations were - I'm not sure there was enough
22 difference to say that that was actually significant.

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1 ACTING CHAIR BORER: The issue -

2 DOCTOR LINDENFELD: I don't really remember
3 that.

4 ACTING CHAIR BORER: - well, whether it was
5 or - whether it reaches statistical significance or
6 not from the six events -

7 DOCTOR LINDENFELD: Right.

8 ACTING CHAIR BORER: - is not really key.

9 DOCTOR KORBIN: It did, it did reach
10 statistical significance.

11 DOCTOR LINDENFELD: I don't think I'd
12 probably include hospitalizations, I think the numbers
13 are so small.

14 ACTING CHAIR BORER: Yes.

15 The one comment that I would add about
16 that, in response to Bob's question before, is that
17 the way I see it the clinical progression issue is
18 based on the recognition of worsening symptoms, which
19 if, indeed, they occurred could be treated, could be
20 approached by increasing the dose within the label.
21 So, until we have some evidence that there's something
22 more than hospitalizations for worsening symptoms, I

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1 don't think we have a basis for suggesting that people
2 should take a higher dose because natural history is
3 going to be altered. One could say that, but we have
4 no data to base that on. But, that's another issue
5 here.

6 Okay. So, JoAnn has identified what seem
7 to be areas where we can say something about here.

8 Does anybody have anything to add?

9 DOCTOR LIPICKY: Well, yeah, I guess
10 anticipating a discussion that I might have, should
11 this be in the description of the clinical trials,
12 that's what you were elaborating on, or should it be
13 in the indication section, what can people expect?

14 ACTING CHAIR BORER: On what I elaborated
15 on or what JoAnn elaborated on?

16 DOCTOR LIPICKY: What JoAnn elaborated on.

17 ACTING CHAIR BORER: Okay.

18 DOCTOR LIPICKY: For example, should all of
19 the things that you thought were positive be things
20 that are in the indication. This is indicated to
21 increase your Borg dyspnea scale, or make you less
22 short of breath, or make you walk better, or should

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1 that sort of stuff just be in the description of the
2 trials?

3 For example, captopril is indicated to
4 lower blood pressure, to save life, and decrease
5 hospitalizations. That's in the indications, because
6 that's what the trial found. So, this question, in
7 part, was oriented towards what should be in the
8 indications and what should be in the package insert.

9 DOCTOR LINDENFELD: Well, I feel
10 comfortable with improve exercise capacity and
11 symptoms, and then I would enumerate these things in
12 the description of the trial.

13 DOCTOR LIPICKY: Fine, okay, that's good.

14 ACTING CHAIR BORER: So, the conclusion is
15 that it should be indicated to improve exercise
16 capacity and reduce the symptoms associated with
17 pulmonary hypertension, JoAnn, is that what you said?

18 DOCTOR LINDENFELD: Yes.

19 DOCTOR LIPICKY: Yeah, okay.

20 ACTING CHAIR BORER: Okay. That's in the
21 indication section, and with the description of the
22 trial give that combined progression endpoint?

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1 DOCTOR LIPICKY: Well, I don't think we
2 have any combined progression.

3 DOCTOR FLEMING: Okay, what do we do with
4 the endpoints, death, hospitalization, discontinuation
5 for worsening, because if you look across the two
6 studies this composite endpoint, each of the elements
7 goes in the right direction, so when you look together
8 as a composite you get a difference on the order of p-
9 value of .01 log rank test in the 352 study, in the
10 351 study you get a p-value of .03. So, both studies,
11 on a predefined and clinically, very important
12 composite endpoint, show significance.

13 Now, we can't say, of course, exactly as
14 JoAnn said, there's not proof that there's an effect
15 on death, but when you look at, there are two versus
16 one, versus zero on deaths, 9, 3, 3 hospitalizations,
17 6, 3, 2 on worsening, three hospitalizations in the
18 second trial, you put all this together and by my
19 crude calculation the rate of this very important
20 composite endpoint in the two studies is reduced from
21 about 21 percent to about 5-1/2 percent, so about a
22 fourfold reduction. And, individual studies each

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1 yield p less than .05, so where do we go with that?

2 DOCTOR LIPICKY: Well, that's a very
3 important decision to make, as to where that goes I
4 the label. It sort of doesn't really matter too much,
5 but I will have the argument as to whether it should
6 or should not go into the indications. And, I just
7 wanted to know how you felt, that's all.

8 ACTING CHAIR BORER: Why don't we get
9 everybody's comment, because this is really a major
10 issue.

11 Bob?

12 DOCTOR TEMPLE: Well, just one thought.
13 When you say that it improves exercise tolerance and
14 decreases symptoms, that accounts, at least in part,
15 for the reason you didn't go to the hospital, because
16 you didn't have those things. So, the indication that
17 you describe, to some extent, describes those things
18 in the absence of an obvious mortality effect, that
19 would be a different thing.

20 So, that finding, nonetheless, is
21 interesting and we would be inclined, I think, to put
22 it in clinical trials, but only if you tell us, oh,

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1 no, you absolutely you have to put that endpoint in
2 the indications would we be inclined to put in the
3 indications, because it seems redundant with what
4 you've already got.

5 DOCTOR FLEMING: Well, it's interesting,
6 Bob, I find it reinforcing - I find it a non-trivial
7 additional reinforcement of the strength of evidence,
8 beyond exercise tolerance and symptoms.

9 DOCTOR TEMPLE: No, I totally agree, that's
10 why it should be part of the description of the study
11 results, but would that make you want to change the
12 indications, when to some extent there's some overlap
13 in what it shows and improving symptoms. It tells you
14 it improved them a lot maybe.

15 DOCTOR LIPICKY: I guess in part it would
16 depend on whether you really thought that that was
17 evidence that the natural history of the disease was
18 altered, and it could be, for example, like some drugs
19 we know in heart failure that can make you run longer
20 on treadmills and have all of the right things in
21 terms of hospitalizations even, and in the long run
22 they kill you because they don't favorably influence

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1 the natural history of the disease, but they make
2 people feel better, even though everything is going
3 down hill from there.

4 So, it is a relatively important
5 distinction to make; and I don't think the data - I'll
6 just give you my interpretation - the data that's
7 being looked at doesn't give you a feeling for natural
8 history of disease, it really is just consistent with
9 symptoms.

10 ACTING CHAIR BORER: Okay.

11 Since this is an important issue, we'll
12 get everybody's opinion on the question of, are these
13 data sufficient to alter the indications beyond making
14 people feel better, however you want to word that?

15 Why don't we start at the right-hand side
16 there, Michael?

17 DOCTOR ARTMAN: No, I don't think it should
18 be part of the indications.

19 ACTING CHAIR BORER: Okay.

20 Doctor Anderson?

21 DOCTOR ANDERSON: I agree.

22 ACTING CHAIR BORER: Okay, Steve?

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1 DOCTOR NISSEN: Yes, I concur, but I just
2 wanted to comment, Ray, that it's going to be very
3 hard to show now any alteration in the natural history
4 of the disease, because, frankly, no one is going to
5 do a placebo controlled trial from now on. And so, we
6 are not going to know whether we can actually have
7 these very long-term effects on the sort of natural
8 progression of the disease. It's unfortunate, because
9 I think that this drug might have the potential to do
10 that, we're just not going to know.

11 DOCTOR LIPICKY: So, you are addressing my
12 question to you, as to whether we made a mistake
13 letting them do a symptom trial only?

14 ACTING CHAIR BORER: No, no, he's just
15 saying the answer is no, and we may not get -

16 DOCTOR LIPICKY: But, I heard him
17 criticizing us rather significantly.

18 ACTING CHAIR BORER: No, he wasn't.

19 DOCTOR NISSEN: No, I wasn't, Ray.

20 DOCTOR LIPICKY: You should have been.

21 DOCTOR NISSEN: You know, I just want to
22 say that I wouldn't change the label, but -

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1 DOCTOR LIPICKY: That's fine.

2 DOCTOR NISSEN: - I think, you know, we
3 may have an effect here on the natural history of the
4 disease, and we may never know because it's not going
5 to be possible to find out.

6 DOCTOR HIRSCH: Not totally impossible, but
7 unlikely. That's what historical controls are for,
8 you'll know if it's big.

9 ACTING CHAIR BORER: That's not our role
10 today. Let's continue with the indications.

11 DOCTOR BREM: I don't believe that
12 mortality and hospitalization rate should be in the
13 indications.

14 ACTING CHAIR BORER: My vote is no, too,
15 and I would suggest that in a study that looks at dose
16 response one might be able to see some evidence that
17 the drug actually alters natural history, if you
18 studied enough people. So, it is possible to still
19 give benefit, I think, with this drug, and still look
20 at other issues without having to use a placebo that
21 will no longer be possible.

22 Tom?

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1 DOCTOR FLEMING: So, essentially, what my
2 colleagues are saying is that these data are
3 importantly reinforcing the exercise tolerance and the
4 symptom results, but, essentially, what we would
5 really need to be able to say we are altering the
6 natural history of the disease in ways that ultimately
7 would influence endpoints such as mortality and
8 hospitalization, we would need a much larger and much
9 longer experience, is that, essentially, what we are
10 hearing?

11 DOCTOR LIPICKY: Right.

12 ACTING CHAIR BORER: Particularly,
13 mortality.

14 DOCTOR FLEMING: And, I accept that.

15 DOCTOR LINDENFELD: I agree with everyone
16 else.

17 DOCTOR ARMSTRONG: My view would be that to
18 be fair to the sponsor, in the product description one
19 could say that in support of the indications
20 predefined clinical worsening was significantly
21 reduced in a modest number of patients, without an
22 effect on death. So, I don't have a problem with

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1 describing what was predefined and found as supportive
2 evidence in the product description, but I agree it
3 shouldn't be in the indications.

4 ACTING CHAIR BORER: Alan?

5 DOCTOR HIRSCH: I'd just concur, I think
6 it's a description of findings, it's not an
7 indication, and to say we are not slaves to p-values
8 it's very, very exciting data. It could be assessed
9 further, but I would need larger numbers and
10 adjudication.

11 ACTING CHAIR BORER: Considering all
12 pertinent data - that's a unanimous vote, I think -
13 considering all pertinent data is bosentan an
14 effective treatment for pulmonary hypertension? I
15 think we've already said it is. Over what period of
16 administration are the benefits of bosentan manifest?

17 JoAnn?

18 DOCTOR LINDENFELD: We know for sure about
19 over a 16-week period.

20 ACTING CHAIR BORER: Okay.

21 Anybody disagree with that?

22 DOCTOR HIRSCH: Can I ask, so you don't

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1 think the extension part of it provides further
2 support?

3 ACTING CHAIR BORER: Why not 28?

4 DOCTOR LINDENFELD: Well, I think it
5 provides further support, but I'm most comfortable
6 with the 16-week data.

7 DOCTOR TEMPLE: That certainly was a better
8 than usual follow-on study than we've seen, that's for
9 sure. The question is whether it's enough.

10 ACTING CHAIR BORER: Tom, what do you think
11 about the strength of that evidence?

12 DOCTOR FLEMING: Well, it's strikingly
13 different from some previous experiences that we've
14 had. Contrary to what I might have said in previous
15 experiences, this data set you had nearly uniform
16 follow-up, and so the biases that I worried about on
17 those other settings aren't here. This is
18 interpretable data, because nearly everybody in the
19 original studies were, in fact, included in the
20 extension trials, so you are able to really get a more
21 reliable sense of what benefit to risk is here.

22 ACTING CHAIR BORER: Right, so why not

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1 reward that?

2 DOCTOR TEMPLE: There was also a withdrawal
3 component at, I guess, 16 weeks, that showed that at
4 that point if you took the drug away, so that might be
5 said to give somewhat more credibility to the ones who
6 persisted in having an effect after that time.

7 ACTING CHAIR BORER: Steve?

8 DOCTOR NISSEN: I really think the sponsor
9 has made the case for the benefits over 28 weeks, and
10 I think, you know, when you do a study this carefully,
11 and you've got really high follow-up, we ought to say
12 that. And so, I strongly support the 28-week
13 statement.

14 ACTING CHAIR BORER: JoAnn, what do you
15 think?

16 DOCTOR LINDENFELD: I think I'm comfortable
17 with that.

18 ACTING CHAIR BORER: Okay.

19 Anybody not comfortable? No? Okay. So,
20 we've now said the duration of the trial is what we
21 can talk about, and that's 28 weeks, half a year.

22 Over what dose range are the benefits of

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1 bosentan manifest? We've spent a great deal of time
2 talking about that. JoAnn, what do you want to
3 summarize on this?

4 DOCTOR LINDENFELD: I don't think we really
5 have a dose range. I think we know that 125 mg twice
6 a day is effective.

7 DOCTOR LIPICKY: Why wouldn't you say
8 overall dose range, all doses studied? Do you think
9 some dose was studied that didn't work?

10 DOCTOR LINDENFELD: Well, no one is asking
11 for 250 mg, so I don't have to consider that.

12 DOCTOR LIPICKY: Well, we don't care what
13 they are asking for.

14 DOCTOR LINDENFELD: Okay.

15 DOCTOR LIPICKY: They are going to get 250
16 anyhow.

17 ACTING CHAIR BORER: We care a little.

18 DOCTOR LINDENFELD: You know, I don't think
19 we have clear data that 62.5 milligrams is effective.

20 DOCTOR LIPICKY: Oh, so then you wouldn't
21 give that.

22 DOCTOR LINDENFELD: I would start with it.

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1 DOCTOR LIPICKY: Well, how can you start
2 with it if you don't know it works?

3 DOCTOR LINDENFELD: Because that's how the
4 protocol was done.

5 DOCTOR LIPICKY: So then, you must think it
6 does something.

7 DOCTOR LINDENFELD: Because it's been
8 suggested that to start low and build up, so I think
9 I would start with that.

10 Now, what would I recommend? I don't have
11 data to recommend 62.5 mg, but -

12 DOCTOR LIPICKY: Right, you have no data to
13 recommend any dose, but you don't think that any dose
14 studied, in fact, was shown to be ineffective, do you?

15 ACTING CHAIR BORER: We have four-week
16 data.

17 DOCTOR LINDENFELD: No, I can't make that
18 judgment.

19 ACTING CHAIR BORER: We have four-week data
20 about 62.5, because that's where everybody started.

21 DOCTOR LINDENFELD: Right.

22 ACTING CHAIR BORER: I mean, we couldn't

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1 say anything about more than four weeks, but we do
2 know that it's effective for four weeks.

3 DOCTOR LINDENFELD: Four weeks, right.

4 DOCTOR LIPICKY: Better than placebo.

5 ACTING CHAIR BORER: Better than placebo
6 for four weeks, yeah.

7 DOCTOR LINDENFELD: For exercise time.

8 DOCTOR LIPICKY: Yes, sure, only -

9 DOCTOR LINDENFELD: Only exercise time.

10 ACTING CHAIR BORER: I mean, we do -

11 DOCTOR LINDENFELD: We don't have the other
12 supporting -

13 ACTING CHAIR BORER: - well, that's right,
14 we don't have all the other stuff, but we do have four
15 weeks worth of data, and, you know, one might think
16 that it would be reasonable to say that from what we
17 have it's not ineffective, at least for the early time
18 period.

19 I don't know, Steve?

20 DOCTOR NISSEN: You know, I think you have
21 to look at the data, and I think that the three doses
22 that were looked at appear effective, 62.5, 125 and

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1 250, and I think it would be reasonable to say all
2 those doses were proven effective, and to make some
3 comment on the increasing incidence of abnormalities
4 in liver functions at the higher doses. And, I think
5 that clinicians can make an appropriate risk benefit
6 assessment.

7 To me, that's logical. I think, you know,
8 we've seen efficacy at the 250 dose, and to me I think
9 that all three doses have been shown to be effective.

10 DOCTOR LINDENFELD: Well, I don't - Tom has
11 got the data here, but I don't think at four weeks it
12 was statistically significant, in terms of even
13 exercise time.

14 DOCTOR FLEMING: Right, what JoAnn is
15 noting, and if we look at the walk distance data from
16 352, where we have the most information, this is page
17 25 in the efficacy assessment toward the back, figure
18 two, what we see, and we've seen this with other
19 related interventions as well, there is this placebo
20 effect, and so the actual signal that you see at the
21 first assessment is less. I don't know if it's
22 significant, but it's certainly much less. It may

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1 well be that 62, if continued, would have, over a
2 period of 12 or 16 weeks, shown effects, but that's
3 somewhat speculation.

4 My sense is, these studies were well
5 designed and they address two specific regimens, 62.5
6 going to 125, and 62.5 going to 250, and they clearly
7 showed efficacy at both of those regimens. That's
8 what we know.

9 It's speculation whether or not efficacy
10 would have been maintained with 62.5 if it hadn't been
11 increased.

12 ACTING CHAIR BORER: Would it be fair to
13 describe the data somewhere in the label and to
14 suggest that it's not unreasonable to start with the
15 lower dose, because, again, the primary goal here is
16 to make people feel better. If they feel better, they
17 win.

18 DOCTOR LINDENFELD: Well, I think you sort
19 of have to start with that dose, that's how the
20 studies were done, and how do we know that it's safe
21 to start at a higher dose? We don't have any data
22 there in these patients, I don't think you can start

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1 at a higher dose.

2 ACTING CHAIR BORER: The question is,
3 should you stay on it after four weeks?

4 DOCTOR LIPICKY: The question is -

5 ACTING CHAIR BORER: And, on some important
6 questions you have no data at all, like
7 hospitalizations.

8 DOCTOR LIPICKY: - so that means the
9 instructions for use must insist that, even if people
10 are doing swell on 62.5, they have to take 125.

11 DOCTOR FLEMING: Well, Ray, that's
12 different than the question you are asking us. You
13 might want us to ask that.

14 DOCTOR LIPICKY: If we have no confidence
15 that 62.5 works, how could we recommend that in any
16 individual they be kept on it?

17 DOCTOR FLEMING: Question 1.5 says, over
18 what dose range are the benefits manifest?

19 DOCTOR LIPICKY: Right.

20 DOCTOR FLEMING: And, we had two specific
21 regimens, and the benefits were manifest for both of
22 those regimens.

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1 Now, we can go beyond that and say, well,
2 what about the setting where someone starts at 62.5
3 and has very good symptomatic improvement, are they
4 entitled to stay at that lower dose? Well, that's -
5 we don't know for a fact that we have proven efficacy
6 there. It certainly would be their judgment, and the
7 clinician's judgment, to do so if they choose.

8 DOCTOR LIPICKY: So, I guess the right
9 question here would have been, do you think 62.5 is
10 not part of the continuous dose response curve that
11 was seen with bosentan, would that be a better
12 question?

13 DOCTOR FLEMING: We do not have direct
14 evidence to answer that. You can speculate that it
15 may well be that it provides - it would provide
16 substantial symptomatic improvement to a meaningful
17 fraction of the population.

18 DOCTOR LIPICKY: But, you don't know.
19 Okay.

20 ACTING CHAIR BORER: Okay. Maybe we can
21 get back to this when we get to other sections of
22 these questions, but, you know, I would make the plea

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1 again, I mean, yes, we don't know if it will prevent
2 hospitalizations, but as you pointed out, Bob, and as
3 I think we've all agreed, hospitalizations for
4 increasing symptoms are an extension of symptoms.

5 DOCTOR TEMPLE: Yes, but it's a matter of
6 degree, for example, the smaller effect, if, indeed,
7 it is smaller at 62.5, might not get you that benefit.
8 There's no way to know.

9 ACTING CHAIR BORER: It might not, but
10 you'd know it the first time you went to the hospital.
11 You could increase the symptoms, if the symptoms got
12 worse you could do that and prevent a hospitalization
13 if that's really possible, by increasing the dose
14 while you are following the patient as an out patient.
15 I mean, you could.

16 Steve?

17 DOCTOR NISSEN: I don't see how we can
18 suggest that a dose is effective that we have no proof
19 of efficacy for. I mean, as prudent as it may seem to
20 leave somebody at 62.5 mg for the safety reasons, I
21 mean, I just can't imagine why we'd want to suggest to
22 the medical community that there is an effective dose

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1 that is less than the dose that was proven to be
2 effective in these clinical trials.

3 ACTING CHAIR BORER: I guess the reason
4 that I would suggest, and you might accept and you
5 might not, and we can sort of get a sense of the
6 committee here and leave the FDA to deal with it, is
7 that what we are hoping - no, what we know we can gain
8 here is symptom benefit. We don't know that we can go
9 beyond that to mortality, alteration in longevity, da,
10 da, da, da.

11 Since we don't know that, and since, as
12 you pointed out, there are potential problems that are
13 dose related, it seems not only prudent, but
14 appropriate, to begin with the lowest dose that we
15 have reason to expect should have some beneficial on
16 the endpoint that we know we can offer people. And,
17 if they get that endpoint, if they feel better, isn't
18 that a good thing?

19 The only reason to push higher, to mandate
20 going higher, would be the belief that you are going
21 to give them more than just feeling better, and maybe
22 we all believe that based on the data we've seen, and

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1 if we do, then we have to do that.

2 Steve?

3 DOCTOR NISSEN: There's a fundamental
4 problem with that, and the fundamental problem is the
5 placebo effect. You know, this is not a placebo
6 controlled, you know, environment once this drug is
7 out there. And so, if I say to a patient, I'm going
8 to give you a drug that's going to make you feel
9 better, 30 to 40 percent of them are going to feel
10 better. And now, they stay on a dose that has not
11 been proven to be efficacious for the primary endpoint
12 of the clinical trials. And so, I think it's a
13 slippery slope here, and I think we have to stay with
14 those doses that improve the six-minute walk test in
15 a statistically significant way, and to suggest less
16 than that may be a disservice to patients with this
17 disorder.

18 DOCTOR LIPICKY: We'll see, that thinking
19 process, the thinking process you are going through,
20 is one of the principal reasons that people don't want
21 to look for less than some maximally effective dose,
22 and say to identify a dose less than that, because if,

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1 in fact, it doesn't work quite as well to say that it
2 works better than placebo takes a very large sample
3 size. So, consequently, the thinking process you are
4 going through forces people who are developing drugs
5 to not describe doses that may be appropriate to use,
6 better than placebo, but less than maximal effect. And
7 so, you get to the situation where people want to
8 study the maximally tolerated dose versus placebo
9 only.

10 So, I'm not comfortable with that logic,
11 because it encourages very bad drug development.

12 DOCTOR NISSEN: Ray, the only problem is,
13 is I think it has to be in the disease context, and we
14 are talking about the context of a very nasty disease.

15 DOCTOR LIPICKY: That is not disease
16 context dependent at all.

17 DOCTOR NISSEN: Well, I guess the risk
18 benefit becomes a little bit different when you are
19 not -

20 DOCTOR LIPICKY: It's a disease - you have
21 no risk benefit data here at all, with respect to real
22 risk, morbid/mortal. So, we are just talking playing

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1 around. Okay. So, you know, I don't think this is
2 disease specific at all.

3 ACTING CHAIR BORER: We probably can't
4 give you a precise consensus answer on this, but at
5 least you should hear from everyone on the committee
6 how they think the dose issue should be handled in the
7 label.

8 Let's start at the left side of the table
9 this time. Alan?

10 DOCTOR HIRSCH: Well, this time I don't
11 feel very confused, although I hear the controversy.
12 Aren't we always in the same position, where what we
13 need to do is describe how the trial was conducted,
14 including the dose escalation, state that benefits
15 were achieved, or reported at the 125 and 250 doses,
16 physician's discretion will be used to determine
17 whether dose titration should occur in individual
18 patients.

19 ACTING CHAIR BORER: Okay.

20 Paul?

21 DOCTOR ARMSTRONG: So, with starting at
22 62.5, which we've agreed must be done, again I would

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1 reiterate that because of the toxicity effect
2 relationship with this agent my view would be that
3 clinicians should assess at four weeks the need to up
4 titrate based on the clinical response of the patient.

5 ACTING CHAIR BORER: Okay.

6 JoAnn?

7 DOCTOR LINDENFELD: I still think we need
8 to describe how to use the drug the way it was used in
9 the study.

10 ACTING CHAIR BORER: Okay.

11 Tom?

12 DOCTOR FLEMING: I agree with JoAnn, we
13 should indicate what was done in the clinical trial,
14 and the two regimens that were assessed in the trial
15 that were found to be effective were the 62.5 going to
16 125, and the 62 going to 250. That's what we know.
17 That's what we should indicate.

18 ACTING CHAIR BORER: Mike?

19 DOCTOR ARTMAN: Yes, I agree with what's
20 been stated at the left-hand side of the table.

21 ACTING CHAIR BORER: Wait, there are two
22 different statements on the left-hand side of the

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1 table.

2 DOCTOR ARTMAN: The latter.

3 ACTING CHAIR BORER: It's two and two.

4 Okay, so you are agreeing with Tom and JoAnn.

5 DOCTOR ARTMAN: Right, yes.

6 DOCTOR ANDERSON: I don't have any
7 additional comments.

8 DOCTOR NISSEN: I agree with the position
9 articulated by Tom and JoAnn.

10 DOCTOR BREM: I do as well.

11 ACTING CHAIR BORER: Okay.

12 For whatever it is worth, I would have to
13 agree with Alan and Paul that we should describe what
14 was done. We should tell people what the two dosing
15 regimens are and what resulted from them, but I think
16 there has to be some wording in there that indicates
17 that we are talking about symptom relief, and that
18 when we get to it there is a potential toxicity issue
19 and the clinical judgment has to be used in escalating
20 from the starting dose.

21 Okay. So, the sense of the committee is
22 really that there are two regimens, but you have a

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1 minority group that's suggesting that a little bit
2 more ought to be put in the label.

3 Let's see, where are we here.

4 Number two, did the dose of bosentan rise
5 steadily during treatment?

6 Okay, JoAnn, why don't you go ahead and go
7 through that one.

8 DOCTOR LINDENFELD: Well, I think we've
9 discussed this. The dose did rise, but that was
10 protocol specified, and really all we know was the
11 protocol specified dose increase.

12 ACTING CHAIR BORER: Okay.

13 Is there - are these data, or the lack
14 thereof, an approval issue?

15 DOCTOR LINDENFELD: I don't believe so.

16 ACTING CHAIR BORER: If bosentan were
17 approved, how should the label describe this? We just
18 talked about that.

19 DOCTOR NISSEN: I just wanted to make one
20 comment that would have been, I think, extraordinarily
21 useful in the development. This was a superb
22 development program, but something that might have

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1 given us a signal, since we know in this disease that
2 the hemodynamic changes track pretty well with what
3 ultimately happens with symptoms, if we had had even
4 small scale dose ranging studies with hemodynamic data
5 it might have given us a much stronger signal as to
6 what doses ought to be tested.

7 And, you know, I'm not suggesting that the
8 hemodynamics are sufficient for approval, but they may
9 be very helpful in dose ranging, and I think not going
10 through that step as meticulously as they might have
11 done we might have found out that there wasn't -
12 supposed you found out there wasn't very much
13 hemodynamic change at 62.5 mg, wouldn't that be
14 helpful in designing studies?

15 So, I think it's something to think about
16 in the future.

17 DOCTOR LIPICKY: Not at all.

18 ACTING CHAIR BORER: Can you expand on
19 that, Ray?

20 DOCTOR LIPICKY: No, well, that would just
21 delay things. You have no idea why people's symptoms
22 got better, so, therefore, seeing no acute change in

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1 pulmonary artery pressure at 62.5 mg wouldn't convince
2 me that it should not be a study dose, because I have
3 no idea why these people felt better, and I would feel
4 much better if, in fact, some dose had been studied
5 that didn't affect the pulmonary artery pressure.
6 Then I could address your question.

7 So, I don't think that that's sensible in
8 any way, shape or form.

9 ACTING CHAIR BORER: Okay.

10 DOCTOR LIPICKY: Unless you want to do this
11 kind of development program which focuses on a dose,
12 then you pick the dose that gives you the maximum
13 hemodynamic effect. That's what was done. And, I
14 don't think you want to encourage that, but maybe you
15 do.

16 ACTING CHAIR BORER: Number three, safety
17 issues.

18 JoAnn, bosentan as a teratogen, is this an
19 approval issue?

20 DOCTOR LINDENFELD: I don't believe it's an
21 approval issue. I think most of the patients are
22 women and most of them are encouraged not to become

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1 pregnant, and many are aborted if they do become
2 pregnant.

3 But, it is a significant issue, again, to
4 just bring up the point that one would see teratogenic
5 effects before one would know they were pregnant.

6 ACTING CHAIR BORER: How important is this
7 as a labeling issue? Is this a black box issue?

8 DOCTOR LINDENFELD: I think it is a black
9 box issue, yes.

10 ACTING CHAIR BORER: Okay.

11 DOCTOR FLEMING: Essentially, then, do we
12 encourage women to get a pregnancy test then before
13 they would start therapy?

14 DOCTOR LINDENFELD: Good question. I guess
15 I'd have to ask, but I would think that would
16 certainly be reasonable, and then - the counseling is
17 already done routinely with these patients.

18 DOCTOR HIRSCH: Counseling is different
19 than starting - casual counseling, because we know
20 that this is a dangerous disease, is different than
21 applying a medication that will directly damage
22 developing humans.

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1 DOCTOR LINDENFELD: Right.

2 DOCTOR HIRSCH: What does the sponsor say?

3 DOCTOR KORBIN: In all of our studies women
4 were tested to make sure that they were not pregnant.

5 DOCTOR LIPICKY: So, that's what the black
6 box will say?

7 DOCTOR KORBIN: I don't think that it is a
8 black box, I just think that -

9 DOCTOR LIPICKY: Well, but that's what was
10 just suggested.

11 ACTING CHAIR BORER: How strongly do we
12 want to phrase that?

13 DOCTOR LINDENFELD: Yes, I guess we could
14 stand some opinions here.

15 DOCTOR KORBIN: We definitely don't want
16 women to get pregnant on this drug.

17 DOCTOR LINDENFELD: This is a big issue.

18 ACTING CHAIR BORER: Okay.

19 Why don't we then get a quick response
20 from everybody. We say this is a labeling issue, is
21 it a black box issue, number one, and, therefore,
22 number two, is it necessary before people start on

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1 this drug, or are prescribed this drug, that the
2 patient and the doctor know the results of a pregnancy
3 test?

4 Mike?

5 DOCTOR ARTMAN: Yeah, it is a black box
6 issue for sure, and since the effect can occur very
7 early the patient should be tested and confirm cannot
8 be pregnant before starting on the medication.

9 ACTING CHAIR BORER: Okay.

10 DOCTOR ARTMAN: Absolutely.

11 DOCTOR NISSEN: I agree.

12 ACTING CHAIR BORER: Doctor Brem?

13 DOCTOR BREM: I agree as well.

14 ACTING CHAIR BORER: Agree.

15 DOCTOR FLEMING: Agree.

16 DOCTOR LINDENFELD: Agree.

17 DOCTOR ARMSTRONG: Agree.

18 DOCTOR HIRSCH: Agree.

19 ACTING CHAIR BORER: Okay, it's unanimous.

20 DOCTOR TEMPLE: Jeff?

21 ACTING CHAIR BORER: Yes.

22 DOCTOR TEMPLE: Do I understand that the

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1 sponsor has proposed patient labeling as well, to be
2 handed out with it, is that correct, a patient insert?
3 Somebody nod. Is there a proposed patient package
4 insert?

5 DOCTOR KORBIN: We did give you a proposal,
6 yes, to the Agency.

7 DOCTOR LIPICKY: Yes, there is.

8 ACTING CHAIR BORER: Yes, okay.

9 Okay, well that's another way to remind
10 people of this obligation.

11 Just a no from anyone who thinks that this
12 warning shouldn't be in the patient label, does anyone
13 think it shouldn't be? No, I take that as a unanimous
14 statement that it should be.

15 Okay. JoAnn, some endothelium receptor
16 antagonists have shown testicular toxicologic findings
17 in animal studies, usually in studies lasting 12 weeks
18 or longer. This may be a class effect. The animal
19 data for bosentan appear in the pharmacology review.
20 There are no pertinent data in humans.

21 If one were to conclude that bosentan
22 exhibited testicular toxicology in animals, would this

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1 be an appropriate issue for a treatment for pulmonary
2 hypertension, and, if so, what prior to approval would
3 need to be known about the following things?

4 JoAnn, why don't you go through all those.

5 DOCTOR LIPICKY: Can I just preamble you a
6 little bit?

7 ACTING CHAIR BORER: Yes.

8 DOCTOR LINDENFELD: No.

9 DOCTOR LIPICKY: And, it's sort of unfair
10 in a way, because we have just reviewed internally and
11 this is not public knowledge, all of the endothelial
12 antagonists that have been submitted in the IND stage,
13 and looked at the animal reproductive toxicology, and
14 are convinced ourselves, without anyone having seen
15 the data externally, that there is a class effect. It
16 depends on dose and duration of administration to
17 animals, and that you have to have fairly long
18 durations and fairly high doses to really have very
19 reproducible testicular lesions in animals, so that we
20 think that this is very real.

21 And, we have not, until recently, come to
22 that conclusion, one. Two, we think what we will be

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1 recommending is that anyone who is studying an
2 endothelial antagonist in the future evaluate sperm,
3 counts, and motility, and whatever other thing you are
4 supposed to measure in males who are taking
5 endothelium antagonists, because there is a potential
6 of the other species - no, the other sex, having
7 similar problems reproductive-wise as the teratology
8 part.

9 And, this is not evaluated at all, but we
10 will be stuck with making a decision here because we
11 know we've come to the conclusion that there is a
12 class effect, and that we don't have any information
13 on what happens to men who are taking endothelium
14 antagonists.

15 ACTING CHAIR BORER: Okay.

16 With that as a preamble -

17 DOCTOR LIPICKY: So, with that, you can
18 look at the questions then, but you need to do that,
19 from my perspective, that I think we will have a
20 problem.

21 ACTING CHAIR BORER: Right.

22 DOCTOR LIPICKY: And, not from the

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1 perspective that you saw, which would make it not seem
2 like it was much of a problem.

3 ACTING CHAIR BORER: Okay.

4 Let's assume that there is a problem that
5 the FDA has now discovered, is this an approvability
6 issue, remembering, of course, that though this is
7 overwhelmingly a problem in women rather than men
8 there are men with pulmonary hypertension, is this an
9 approvability issue?

10 DOCTOR LINDENFELD: I don't believe it's an
11 approvability issue, but it is an issue, and I think
12 we need some more data. I'd have to defer to Ray on
13 what they recommended for this, but we definitely need
14 some more data and then I think the question will be
15 whether or not this needs to go in the black box as
16 well, I suppose, until we have more data.

17 ACTING CHAIR BORER: What do you think
18 about that? Do you think it should?

19 DOCTOR LINDENFELD: I think it probably
20 should.

21 ACTING CHAIR BORER: How would you write
22 that warning?

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1 DOCTOR LIPICKY: Well, from the information
2 - mind you, I really hate to do this, but I think I'll
3 just give you our conclusions from, you know, in rats,
4 and other species, not just only rats, it looks like
5 you can wipe out the testicles in their entirety.

6 DOCTOR LINDENFELD: Right.

7 DOCTOR LIPICKY: And now, in fact, rats
8 seem to reproduce pretty well without any testicles,
9 so - well, they are very - I don't know why that is.

10 DOCTOR FLEMING: There's a study for you.

11 DOCTOR LIPICKY: But, in fact, what that
12 means is that we need to have some kind of functional
13 test in man, and no one has done that. We haven't
14 recommended that it be done, and at the moment we
15 don't know what the implications of this are, except
16 that they are very real, they are very dramatic, and
17 they are pretty -

18 ACTING CHAIR BORER: Can I suggest then,
19 Ray, with JoAnn's consent, that, you know, we think
20 this is not an approvability issue, but a major
21 labeling issue. We don't have enough information to
22 be able to suggest specific resolution.

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