1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (12:31 p.m.)

3 ACTING CHAIRMAN BORER: It is now 12:31

4 and a half. So we're a minute and a half behind,

5 which we cannot be.

6 Jay, would you give the benefit-risk

7 discussion, please? And then we'll have whatever

8 additional questions we have, and we'll go into the

9 structured review.

10 DR. COHN: All right. Thanks, Jeff.

11 I thought it would be appropriate to kind

12 of place Val-HeFT in perspective with what we have

13 already learned about heart failure and then how this

14 should impact upon the management of the syndrome.

15 So if you'll bear with me for a few

16 minutes, let me first review for you where we have

17 come in the management of heart failure.

18 The first trial I was involved in, and of

19 course, it was the first trial carried out in heart

20 failure was V-HeFT 1, and at the time that we

21 introduced that trial, the one-year mortality in the

22 placebo group in V-HeFT 1 was about 20 percent, and we

23 were really focused on reducing mortality as a primary

24 endpoint in this disease. Twenty percent of people

25 were dying each year with the disease.

1 By the time we got to V-HeFT 2, having
2 been introduce to hydralazine and nitrate and did the
3 solve trial, the placebo arm had now exhibited a lower
4 mortality, right, a better cumulative survival. So we
5 were clearly down moderately in mortality.
6 In Val-HeFT, the one year mortality was
7 nine percent. So we've made actually remarkable
8 impact on this syndrome. Even in the absence of the
9 new therapies, this is the placebo arm in Val-HeFT,
10 and we're getting closer and closer to the
11 epidemiologic data on the predicted survival in
12 nonselected 65 year old white males.
13 So the room for further benefit is still
14 there, but the magnitude of efficacy that we can hope
15 to achieve with further trials in patients with
16 advanced heart disease is limited, and let's face it.
17 All of these trials enter patients with left
18 ventricular remodeling. They've had their disease for
19 years. They're sick. We're not going to restore
20 these people to a normal life expectancy, but we've
21 already made a rather dramatic impact.
22 And I think when you look at the
23 prevalence of this disease, five million people in the
24 United States estimated to have the disease, 500,000
25 new patients per year, we're dealing with a very

1 monstrous public health problem, and if, indeed, 91
2 percent of these people are going to survive each
3 year, which is what Val-HeFT told us, then is it not
4 time to stop focusing on the nine percent who die and
5 begin focusing on the 91 percent who are alive who
6 suffer from impaired quality of life, recurrent
7 hospitalizations, frequent office visits, and
8 incredible cost of health care?
9 Now, remember in Val-HeFT there were four
10 days per year per patient hospitalized. If we have
11 five million patients, that's 20 million days in the
12 hospital per year in the United States alone. So
13 producing a decrement in that hospitalization is of
14 potentially important public health, as well as a
15 personal benefit.
16 So I'm proposing, and this is not new.
17 I've been preaching this way for a long time. So this
18 is merely further evidence for my position, that
19 mortality should not, cannot long serve as the marker
20 for efficacy of treatment in a disease like heart
21 failure.
22 Now, I would love to be able to monitor
23 the biological process, and Ray has heard me preach
24 this many times, and we may not be there yet, but we
25 used all of the tools at our disposal in Val-HeFT to

1 get a sense of the biological process, and they all
2 turned out favorable.
3 So I think we're getting closer and closer
4 to being able to understand this disease and deal with
5 it before people die and intervene effectively to
6 alter the quality of life by altering the biological
7 process.
8 Now, let's look at where we've come now.
9 This is fascinating data analysis from Val-HeFT which
10 to me is the most impressive piece of data in the
11 whole study, even though it's not necessarily
12 randomized therapy. Let's look at the morbidity in
13 Val-HeFT.
14 This is the morbidity in patients who were
15 for reasons only their physicians know, being treated
16 with neither an ACE inhibitor or a beta blocker.
17 Almost 50 percent of them have had a morbid event
18 during the course of the study.
19 This is the group of patients who are on
20 an ACE inhibitor, but not on a beta blocker, and their
21 morbidity was quite a bit lower. We've made a fairly
22 important benefit by adding an ACE inhibitor.
23 And then, of course, we also have a group
24 of patients who are on a beta blocker, but not on an
25 ACE inhibitor, and they also exhibited a benefit,

1 further evidence in a non-randomized way that giving
2 an ACE inhibitor or a beta blocker is good treatment
3 for heart failure.
4 Now, let's look at the group that were on
5 both drugs. Look at this. Their morbidity has been
6 reduced to about 20 percent. This is the best therapy
7 for heart failure, and we should continue to
8 aggressively attempt to get patients with heart
9 failure on ACE inhibitors and beta blockers, and to me
10 this is kind of the nicest data we've even got because
11 this isn't part of a randomized trial. This is real
12 world use of these drugs.
13 Now, let's see what Val-HeFT did to these
14 four subgroups. In this group a striking reduction in
15 morbidity, p, .0033. In this group who were on ACE
16 inhibitors, but not on a beta blocker, a significant
17 reduction, p of .0019. In this group that were on
18 beta blockers, but not on an ACE inhibitor, a rather
19 dramatic reduction, statistically significant even
20 though the group is a small sample.
21 And this is our favorite little whipping
22 boy here, the patients who are already on an ACE
23 inhibitor and a beta blocker, and lo and behold, as
24 we've already pointed out, it went in the other
25 direction.

1 So these three groups exhibit a striking
2 benefit on morbidity, mostly on hospitalizations, and
3 of course, mostly having a major impact on the 20
4 million hospital days, I guess, that occur in the
5 United States each year for worsening heart failure.
6 Well, what about getting everybody on ACE
7 and beta blockers so we don't need to use valsartan?
8 That would be wonderful.
9 The estimated drug usage in the United
10 States today of these drugs is that ACE inhibitors are
11 employed in somewhere between 50 and 75 percent of the
12 population. Remember in Val-HeFT it was 93 percent,
13 but that's not representative because those on an ARB
14 were excluded, and that was also highly specialized
15 heart failure centers.
16 So in the real world it's 50 to 75
17 percent.
18 Beta blocker use, the estimate is
19 somewhere between ten and 25 percent. Well, what's
20 the matter with the practicing community? Don't they
21 know that the ACE and the beta blocker is effective
22 treatment?
23 Well, I guess they do and they don't. Why
24 are more patients not being treated with ACE
25 inhibitors and beta blockers?

1 Well, number one, I guess, is physician
2 education and the pharmaceutical industry is out there
3 promoting these drugs. So it isn't a hidden message.
4 Yet it hasn't had as big an impact as we might have
5 thought.
6 Patient compliance. Patients are told to
7 take drugs, and they don't have a good idea why
8 because their physicians don't really know why, except
9 that it was shown in a trial to reduce mortality.
10 Patients want to feel better, and these drugs like
11 beta blockers often don't. In fact, they have a
12 period of time when they may feel worse.
13 There's wide perception about drug
14 intolerance. Cough with ACE inhibitors, renal
15 dysfunction with ACE inhibitors, hypotension,
16 bradycardia, side effects that cause patients not to
17 want to take pills; co-morbidity which excludes drugs,
18 chronic obstructive lung disease,peripheral vascular
19 disease, et cetera.
20 And with beta blockers particularly, the
21 need for careful drug titration, that many primary
22 care physicians do not want to undertake. So my view
23 is that although we should continue to work on all of
24 these issues and reassure physicians and patients of
25 the importance, we are not likely to markedly improve

1 the compliance with the currently recommended drugs
2 which appear in every consensus document and
3 recommendation. They are still not as widely used as
4 they could be.
5 So is there room then for addition of a
6 new drug like valsartan, which is perceived to be very
7 well tolerated and is well tolerated, does not need
8 careful -- as careful drug titration, and can reduce
9 some of the burdens that the heart failure patient
10 undergoes?
11 So here is my algorithm, if you will, for
12 the current management of heart failure. Patients
13 with heart failure are generally treated with
14 diuretic, and they may be treated with digoxin. They
15 also may be treated with nitrates and hydralazine.
16 I'd like them to be, but Ray hasn't seen fit to give
17 us permission to market it for that purpose. Is that?
18 (Laughter.)
19 DR. COHN: They may be given
20 spironolactone, as has been suggested, although it's
21 particularly advanced Class III and IV, but they will
22 be on all kinds of background therapy. We think that
23 everybody with heart failure, if tolerated, should be
24 on an ACE inhibitor. If they tolerate the ACE
25 inhibitor, they should be given a beta blocker. And

1 if they tolerate the beta blocker, they should be
2 monitored.
3 This is optimal therapy for heart failure.
4 Are we going to get 100 percent of our population on
5 these drugs? No way, no way. There's lots of reasons
6 why, as I've already pointed out to you.
7 If they do not tolerate the beta blocker,
8 I would suggest they be given valsartan based upon the
9 Val-HeFT data, and then they should be monitored on
10 ACE inhibitor and valsartan.
11 If they don't tolerate the ACE inhibitor,
12 they should be given valsartan based on the very good
13 data in Val-HeFT on valsartan in the absence of ACE
14 inhibitor, and if they tolerate valsartan, they should
15 be given a beta blocker and monitored. Now they're on
16 valsartan and a beta blocker.
17 If they don't tolerate valsartan, what
18 should you do? You should give them a beta blocker
19 anyway because the beta blocker is an effective form
20 of therapy, and this is not ideal therapy. Beta
21 blocker alone is not as good as beta blocker with
22 either an ACE inhibitor or valsartan, but it's better
23 than neither.
24 So this is the algorithm then that I would
25 propose based upon Val-HeFT, superimposed on all the

1 data that we've accumulated over the last 15 years,
2 and I believe we can make a major difference now in
3 the outcome in patients with heart failure with this
4 approach to therapy.
5 And I'll stop there. Thank you.
6 ACTING CHAIRMAN BORER: Thank you very
7 much, Jay.
8 Tom you had two overarching questions
9 about efficacy?
10 DR. FLEMING: I think they can be
11 incorporated in my comments at the end in the general
12 review.
13 ACTING CHAIRMAN BORER: Okay. Are there
14 any other questions left for Jay or for anybody else
15 who's presented or hasn't presented?
16 DR. NISSEN: Just one, Jay. You know, one
17 of the problems is, as you've said, we don't know why
18 those patients that didn't get an ACE or a beta
19 blocker didn't, and so in your algorithm, what the
20 algorithm doesn't reflect is the fact that we don't
21 know that the patients that got valsartan in Val-HeFT
22 got it because they couldn't tolerate ACE or couldn't
23 tolerate beta blockers. For some reason or another
24 they didn't get those drugs.
25 DR. COHN: I agree with you.

1 DR. NISSEN: And so it's a gap in our
2 knowledge that doesn't reflect it in your algorithm.
3 DR. COHN: Well, that's true. I can't
4 address the beta blocker story at all because only a
5 third of people were on a beta blocker, and I think
6 that reflects physician judgment to a large extent.
7 I think the ACE inhibitor story is
8 probably a little clearer. This is a population of
9 physicians who really do believe in ACE inhibitors,
10 and since 93 percent of the patients were on it, I
11 suspect, but I agree with you. I can't say that. We
12 have no data to back that up, that the seven percent
13 who didn't were at least perceived to be ACE
14 intolerant; otherwise they would have been on it.
15 But I agree. We have a gap in our
16 knowledge.
17 DR. NISSEN: But it obviously has major
18 implications for how we think about this because
19 because do we think about valsartan as a drug that can
20 be used in ACE intolerant patients? You know, based
21 upon those patients that got it without ACE
22 inhibitors, without really know what their baseline
23 characteristics were. It's a bottom --
24 DR. COHN: You're going to have data in a
25 couple of years from the CHARM trial in which they

1 specifically have a group that are ACE intolerant, and
2 however, I just forewarn you. Given the number of
3 people in the CHARM trial in the ACE intolerant group,
4 it is clearly much higher than any of us ever observe
5 ACE intolerance.
6 So I don't even think you're going to be
7 much off with that database. These are not ACE
8 treated patients, and they're not getting ACE
9 inhibitor for various reasons, and intolerance is the
10 easiest one to identify.
11 ACTING CHAIRMAN BORER: Paul.
12 DR. ARMSTRONG: Jay, two thirds of the
13 Val-HeFT population was on digoxin. Was the effect on
14 hospitalization equally powerful with digoxin versus
15 non?
16 DR. COHN: Yeah, I think it was. That's
17 a good question, and I don't know that we have
18 digoxin/no digoxin data, but we've looked at that, and
19 there didn't appear to be any impact of dioxin on the
20 efficacy of valsartan. Good question though, Paul.
21 ACTING CHAIRMAN BORER: Ray.
22 DR. LIPICKY: As you carefully pointed
23 out, I'm old fashioned, and --
24 DR. COHN: I didn't say that.
25 DR. LIPICKY: It used to be that one made

1 people live longer or feel better, and now there's
2 this morbidity thing that is an index, that is -- or
3 morbidity is counted as hospitalizations, and I don't
4 know where to put that in the spectrum.
5 For example, if one thinks about just
6 feeling better, usually we're fairly hard on the
7 strength of evidence that's required to accept the
8 fact that people feel better , and morbidity is
9 somewhere in between there.
10 How should this be viewed?
11 DR. COHN: Could I have 027? Because I
12 want you to expand your two paradigm concept, Ray.
13 This is the goals for heart failure
14 therapy: make people feel better. That's short term.
15 Prevent people from feeling worse because that's quite
16 different, and what we've shown in Val-HeFT is that we
17 kept people from getting worse because we slowed the
18 progression of the disease.
19 Making people feel better, you can make
20 them feel better with a dobutamine infusion or a
21 milrinone infusion short term because you correct
22 hemodynamics. That's short term benefit.
23 This is the progression of the disease,
24 the second one, that we all recognize is going on
25 under our eyes and in every patient we see unless

1 we're optimally treating them, and that's more of an
2 intermediate term outcome.
3 And, yes, you'll begin to see a reduction
4 of hospitalizations. We saw it within about three
5 months, but the long-term effects really do relate to
6 prevention of progression, and that's delaying death
7 and reducing morbidity, which is hospitalization.
8 DR. LIPICKY: Right. It --
9 DR. COHN: So there's three phases.
10 DR. LIPICKY: If we could talk about that
11 just for a minute longer, you could make people feel
12 better for a long time. It's not necessarily short
13 term, but --
14 DR. COHN: But you have to prevent the
15 progression --
16 DR. LIPICKY: Right.
17 DR. COHN: -- as well as improve the short
18 term. It's two phases.
19 DR. LIPICKY: Now, if you take the
20 prevention of hospitalizations as evidence for
21 altering the natural history of the disease, why don't
22 you affect mortality?
23 DR. COHN: Well, that's a good question.
24 Why don't you affect mortality? We are producing a
25 modest slowing of progression of disease with

1 valsartan.

2 I think valsartan has two components to
3 its efficacy. Now I'm going way beyond the data, but
4 I'm basing this on all my experience. It does have a
5 favorable hemodynamic effect. The BNP comes down.
6 The wedge pressure falls. There is a hemodynamic
7 benefit.

8 That hemodynamic benefit may produce some
9 modest improvement in the way people feel, not enough
10 to improve exercise tolerance with the small sample
11 that we've done. So it's a modest benefit, but it's
12 also slowing progression of the disease even on top of
13 existing therapy. The change in ejection fraction is
14 one percent.

15 You know, with ACE inhibitors it was about
16 three percent. With beta blockers, it was about seven
17 or eight percent. So it's a modest effect, probably
18 not great enough to further reduce mortality on top of
19 existing therapy, ACE inhibitors and beta blockers,
20 but enough to reduce hospitalization, make people feel
21 better, keep them out of the hospital.

22 Is it a gangbuster's drug? Should it
23 replace an ACE inhibitor or a beta blocker? I say no.
24 I think ACE inhibitors and beta blockers do a little
25 more of both. They are hemodynamic, and they improve

1 the left ventricle.

2 Now, if we gave valsartan in the absence

3 of an ACE inhibitor and we showed that, we get a

4 benefit on mortality. So the reason we're not seeing

5 a greater benefit may well be that they're all on ACE

6 inhibitors, but we're getting further incremental

7 benefit.

8 DR. LIPICKY: Right, but I guess I'd just

9 like to press it one more minute. So if you're to

10 take hospitalizations as an index of changing natural

11 history of disease, what you're saying is that the

12 change in natural history of the disease that you can

13 demonstrate may not be enough to affect mortality, but

14 that it should be accepted as changing the natural

15 history of the disease and not as symptomatic care.

16 DR. COHN: Well, to say not affect

17 mortality, I think, is perhaps an overstatement. As

18 you know, when we eliminated that one subgroup who we

19 really believed should not be treated with the drug

20 now, there was a nine percent reduction in mortality.

21 Now, the point estimate was nine percent reduction.

22 The confidence intervals don't tell us

23 anything. Tom is shaking his head appropriately. I

24 mean, that's -- but if we had powered the study like

25 some of reperfusion studies, TPA, et cetera, and found

1 a one percent reduction in mortality and went to the
2 bank with it, you would say, "Gee, that's great," but
3 we'd have to put 40,000 people in the trial.
4 So I'm not sure you wouldn't see -- we
5 can't say that -- but I'm not sure we wouldn't have
6 seen a modest, but small reduction of mortality had we
7 powered this study like the TIMMI trials or the JC
8 trials.
9 ACTING CHAIRMAN BORER: Any other
10 questions or comments? Is there any other comment the
11 company wants to make? Okay.
12 MR. MacNAB: Unless you have specific
13 questions from the company's perspective, I think what
14 you've heard this morning is essentially, you know,
15 our perspective of the trial and some of the ways we
16 think the drug should be used based upon the data of
17 the trial.
18 But I'm here for questions if you have
19 them.
20 ACTING CHAIRMAN BORER: Tom, did you?
21 DR. FLEMING: Yeah, I just had one
22 procedural question unrelated to what we've been
23 discussing while we have the company at the
24 microphone.
25 I was delighted to read in the FDA

1 briefing document that the FDA had requested the
2 minutes of the Data Safety Monitoring Board's
3 meetings, which I think should be an absolute
4 procedure in all settings, in all trials that have
5 data monitoring committees.
6 I was perplexed then to hear that the data
7 monitoring committee didn't produce minutes, which I
8 don't think has ever been a situation in which I was
9 on a monitoring committee that we didn't produce
10 minutes.
11 Can you clarify what happened in this
12 setting?
13 MR. MacNAB: I'd ask Dr. Glazer, the data
14 safety monitoring at endpoint committee. That was,
15 again, an independent committee. So it was probably
16 more independent than you discuss.
17 Why they didn't keep minutes?
18 DR. GLAZER: The DSMB chairman is not
19 here. I think it was their decision not to do that.
20 Again, it was an independent committee. I don't know
21 the precise reason as to why they didn't keep written
22 minutes.
23 DR. FLEMING: Well, I guess in general
24 terms these are very important insights. I would urge
25 that in the future all sponsors insure that their

1 monitoring committees are generating minutes where the
2 open session minutes presumably with recommendations
3 would be disseminated to the sponsor, and the closed
4 session minutes would be archived precisely to allow
5 insights to regulatory authorities and review bodies
6 such as this.
7 ACTING CHAIRMAN BORER: Okay. Well, we'll
8 move on to the structure portion of the session.
9 MR. MacNAB: Could I make just one
10 procedural comment? You have in your questions, I
11 think it's Question 3, which is sort of a statistical
12 question. Once you get into that, will we be able to
13 comment on the comments or would you like us --
14 ACTING CHAIRMAN BORER: Not unless
15 somebody on the committee wants to hear a comment.
16 MR. MacNAB: I mean, because perhaps Dr.
17 Fisher would have some comments on that.
18 ACTING CHAIRMAN BORER: If you have
19 something you want to tell us about now, Lloyd.
20 MR. MacNAB: Yeah, why don't you do that?
21 He can express these things much more
22 elegantly than I will ever begin to.
23 DR. FISHER: Well, I wanted to speak about
24 several things, why I feel the way I do, which you'll
25 hear shortly, but I also wanted to discuss this

1 relative to the two study paradigm. I thought that
2 would come up, and the reason I was trying to flag
3 Malcolm was because I think it will come up in the
4 questions, and I think you will hear a discussion of
5 it.
6 And this is an unusual situation. In most
7 trials where you have a primary endpoint and a
8 secondary endpoint, if you don't meet your primary
9 endpoint, then in a certain sense you're not allowed
10 to look at your secondary endpoints, although there
11 have been some where they were incredibly extreme.
12 Carvedilol comes to mind, which generates
13 a lot of discussion, but you think of it as an
14 exception. Here we met the primary endpoint. There
15 were two of them, but according to the rules
16 adjusting for multiple comparisons, that endpoint was
17 met, but it was met at a level that's somewhat
18 problematic.
19 The two trial paradigm, I've heard some
20 other arguments, but a p value somewhere between
21 .00125 and .0056 is kind of the range you would like
22 to get. But nevertheless we met the primary endpoint,
23 which suggests you can look at the secondary endpoint.
24 Well, the secondary endpoint of
25 hospitalization predefined blows away the p values

1 usually required for the two study paradigm. So this
2 bring up the issue of, well, can you only look at it
3 down to the p value of the primary endpoint.
4 And as far as I know, there's no precedent
5 for this. At least I've never heard it discussed in
6 cardiorenal, but the point I wanted to make is in any
7 event this is not a clear violation, but it's
8 something that's a very subtle statistical point. It
9 deserves consideration.
10 Another thing was Tom looked at all of the
11 signs and symptoms data and said, well, gee, this
12 isn't surprising. They're all correlated.
13 I think I spent more time than Tom
14 thinking about heart failure, and I can assure you I
15 have been in numerous meetings that said can't we find
16 one sign or symptom to show a benefit for the patient.
17 And anybody here that's been involved with heart
18 failure, I'd be amazed if you don't think it's bizarre
19 somehow that these things don't correlate like they
20 should.
21 So I found this amazing. In fact, I think
22 of those signs and symptoms there were five of them
23 that also met the two study paradigm. They were not
24 prespecified secondary endpoints, but again, there was
25 less than .001, adding to the weight of evidence.

1 Some of you know, but I will say it in
2 public. I will not come to a meeting with a sponsor
3 unless I think their compound should be approved, and
4 there have been meetings where I have been invited.
5 I usually don't tell them, "Forget it. I don't think
6 it will be approved." I say, "Well, gee, I'd kind of
7 like to, but I'm busy," or you know, if worse comes to
8 worse, I tell them the truth.
9 And in this particular case, when I was
10 asked, they gave me the data. Nobody talked to me
11 about anything, and I said, "I'm not sure I'll go with
12 you. I want to see how you're going to handle the
13 subgroups."
14 And the subgroup that bothered me, the
15 thing that bothered me immediately was the high
16 mortality in the people on both ACE inhibitors and
17 beta blockers, and certainly we have a number of
18 experts sitting on this panel who could run rings
19 around me physiologically, but my gut reaction was:
20 I think this is true. Somehow it's too much of a good
21 thing.
22 That was just my gut reaction, and not
23 only that. There are a lot of interactions we worry
24 about, but here was one that was significant at the
25 .009 level, and we hadn't looked at all this other

1 stuff when that came up. So we started looking at
2 things.
3 Jay called an ejection fraction
4 independent, and so on. It's not truly independent.
5 It's all part of the same picture, but there are very
6 different parameters, and as you saw, almost
7 everything you looked at went in the same direction.
8 So I would think it would be ridiculous
9 for this committee if you voted for approval to not
10 say to the agency, "Well, I can't stand here and claim
11 absolutely equivocally it's proven it's harmful," and
12 I doubt we'll ever know because I wouldn't picture
13 somebody betting their money on that being a mistaken
14 idea.
15 But when I believe that, there's a flip
16 side to that. That means the other data look better.
17 Now, we don't know how to interpret those p values,
18 and I'm sure Tom is going to get up here, my guess is,
19 and tell us, "Well, gee, in every study even if you
20 have no effect, if you search long enough you can find
21 a subgroup that looks good, and then there's a
22 subgroup that looks bad by complementarity."
23 But this to me was a very different
24 situation. To me, to the extent I understand the
25 biology, it went along with things. There was a

1 question about sample size. I was not involved, but
2 I can almost bet how it went.
3 They went into cardiorenal. Cardiorenal
4 said, gee, congestive heart failure. All drugs either
5 help or kill, and we don't which, and we're not right
6 enough to know which. Unless you get quite a bit of
7 mortality data, we're going to put a black box in
8 there saying this drug may -- Ray can correct me if
9 this is wrong, but I've heard him say it in another
10 context -- there might be 20 percent excess mortality,
11 and so a relative risk of 1.2 or 20 percent often
12 comes up.
13 The sponsor is hoping it works, but at
14 least by powering things for that, you would be
15 attacking in a responsible way the mortality issue,
16 which I think the sponsor has done.
17 So when I put all of this together -- oh,
18 the other thing is the Minnesota living with heart
19 failure questionnaire. I told Jay to push that, but
20 since he helped design it and so on, he thought that
21 was inappropriate, but I really don't think it's the
22 greatest questionnaire in the world for heart failure
23 because it almost never is beneficial. No offense,
24 Jay, but that's --
25 (Laughter.)

1 DR. FISHER: But here's a case where it
2 actually did turn out to be statistically
3 significantly positive, and so all of these things
4 kind of added up in my mind.
5 I don't think you're greatly violating the
6 two study paradigm. If you only focus on the one
7 primary thing and say that's more than .00125, I guess
8 that would be a defensible thing. If Lemm Moyer were
9 here, I would expect to hear it pushed to the nth
10 degree, but I think given that our tradition is if you
11 meet your primary endpoint, you can begin to open
12 things up, and then when you open it up, everything
13 you look at goes in the right direction, and it goes
14 very strongly. It's not just that they happen to hit
15 two signs and symptoms at .02.
16 They had a whole bunch of them at less
17 than .001, and almost all of them were statistically
18 significant. So when you get in your discussion, we
19 have a number of people here who have been involved
20 with congestive heart failure trials. I'd be
21 interested to hear in the discussion how you inject
22 yourselves into that, whether you think my comments
23 make any sense or if that's your experience.
24 For the audience, I'm a know nothing
25 biostatistician. So it's a little bit frightening to

1 get up here and start talking about the clinical
2 things where I hadn't heard a number of points today,
3 and I don't think there will be an opportunity for it
4 to come out later, which is why I'm emoting so much.
5 Thank you.
6 ACTING CHAIRMAN BORER: Okay. Any other
7 points before we move on?
8 It doesn't look like it.
9 We have the structured questions here. I
10 think I'd like to make just one preliminary comment to
11 put this in a framework that at least has meaning for
12 me.
13 I think this was a very interesting
14 development program centered around an extraordinary
15 clinical trial, a landmark study really, and the fact
16 that that study is so powerful, I don't think there's
17 much question that it shows that there's a clinical
18 benefit from the use of this drug in someone, is a
19 tribute to -- the fact that it shows these things and
20 that it was so well done is a tribute to the sponsor,
21 Novartis, and to Jay in directing this and in
22 presenting it as effectively as he did.
23 You know, I wouldn't have guessed that
24 hitting the renin angiotensin system from another
25 angle would have been an easy thing to do and that it

1 would have been highly likely that one could find
2 something even if there was something there to find.
3 And this study did find something, and I
4 think, again, that that's a tribute to the precision
5 and perseverance of the people who were involved in
6 organizing and directing this.
7 So, you know, I don't think there's much
8 question here that there is a clinical benefit. I
9 think the question that we're going to have to focus
10 on is exactly what is the benefit and who benefits,
11 and those are laboring issues, and that's what I think
12 we have to grapple with here today.
13 We've heard several comments about how we
14 might grapple with those things, but I think that the
15 way these questions are written, and they're superbly
16 logical in their sequence of reasoning through an NDA
17 to a final conclusion will lead us to have to conclude
18 how we want to advise the FDA to write a label and if
19 we, indeed, believe Lloyd's argument and everything
20 else and conclude that the drug actually does
21 something.
22 So with that having been said, we'll begin
23 the comments, and our committee reviewer, Tom Fleming,
24 will lead the discussion for most of these questions,
25 I think. He hasn't given a formal review, but he'll

1 give what would have been his formal review in the
2 context of the questions.
3 I will not read the preamble here. I
4 think that everybody has a copy, and you can read it
5 and the sponsor knows what the study was, studies
6 were. They're described here, and the committee
7 knows.
8 So we'll start with the question.
9 Consider the exercise tolerance Studies 110 and 106.
10 In Study 110, all subjects were on ACE inhibitor for
11 at least three months prior to enrollment. Therefore,
12 the subjects randomized to valsartan were withdrawn
13 from ACE inhibitor.
14 What is known about the time course for
15 the loss of effects of an ACE inhibitor on exercise
16 tolerance?
17 Would anybody disagree with me if I said
18 nothing?
19 No. Okay. So the answer, Ray, is
20 nothing, is no.
21 One, point, two. In Study 110, subjects
22 walked 420 meters in six minutes at baseline. What
23 degree of impairment does this represent?
24 Does anybody want to speak specifically
25 about that? I think the answer will be not much, but

1 does anybody want to elaborate on that?

2 No. Okay. That's not an overwhelming

3 impairment it sounds as if.

4 What is known about effects of valsartan

5 and enalapril on exercise can be summarized as

6 follows. We have the table here, enalapril versus

7 placebo. Treadmill is improved. Six minute walk data

8 not available. Valsartan versus placebo, treadmill

9 unaffected from the data we have. Six minute walk, it

10 says no data. There are some, but really versus

11 placebo there's not much.

12 Valsartan versus enalapril. So it doesn't

13 look as if this -- from the way that the question is

14 framed that there's a great deal that we can say about

15 exercise tolerance from the available data, and

16 therefore, what is the effect of valsartan on exercise

17 tolerance?

18 Tom.

19 DR. FLEMING: Well, let me comment, and

20 let me preface my comments by mentioning that as

21 primary reviewer, I think these questions have really

22 laid out to my way of thinking what the critical

23 issues are that need to guide this committee

24 discussion.

25 So in the efficiency of time, I would like

1 to imbed or incorporate my primary review just into
2 these as we go question by question, and before I do,
3 let me just generally reaffirm some of what Jeff has
4 said.
5 I also believe that this study is an
6 extremely informative study. I'm very appreciative of
7 the efforts of the team of investigators and the
8 sponsor in conducting the study, and I would argue the
9 challenge that's facing us is very much getting a
10 sense of not as much about the reliability of results,
11 but the interpretation of results and understanding
12 the populations that may benefit.
13 Relative to this Question 1.3, what is the
14 effect of valsartan on exercise tolerance, and the
15 question is in the context of Studies 110 and 106, 106
16 involving 770 patients looked at exercise tolerance
17 time. Page 78 in the briefing document, FDA, and
18 there's no difference. One, oh, seven, also no
19 difference. Six minute walk test on page 112.
20 Study 110 looked at an active comparison
21 against enalapril with a six minute walk test on page
22 121 and essentially showed roughly comparable results,
23 although the two placebo controlled comparisons say
24 that there is no difference.
25 So essentially -- and I think the

1 sponsor's presentation acknowledged this -- the data
2 from these trials suggests that there was no
3 detectable effect on exercise tolerance.
4 ACTING CHAIRMAN BORER: Okay. Does
5 anybody have any additional comment to make about
6 these?
7 Okay. If not, let's go on to Question 2.
8 Ignoring Val-HeFT, what role did the two studies of
9 hemodynamics and two studies of exercise ability and
10 quality of life have in the case for approval? Do
11 they contribute to demonstration of clinical benefit?
12 Does anybody want to take that? Tom.
13 DR. FLEMING: Yeah, I might comment.
14 Essentially the two studies on hemodynamics, assuming
15 it's 103 and 104, the two studies on exercise
16 tolerance, 106 and 110; the two studies on
17 hemodynamics certainly do provide evidence of effects,
18 for example, on pulmonary capillary wedge pressure.
19 It's my sense that such evidence is relevant to the
20 extent of establishing a biological effect and
21 potentially plausibility of clinical effects, but I
22 think it's very noncontroversial to say that it can't
23 be; it's not a validated surrogate.
24 The two studies on exercise tolerance and
25 quality of life, and we've already alluded to this in

1 the answer to Question 1, the results in 106 and 110
2 on exercise tolerance time were essentially negative,
3 as they were in 110, and the Minnesota living with
4 heart failure questionnaire results in 106 were also
5 negative.
6 So kind of incorporating these issues into
7 the answers to 2.1 and to 2.2, information on quality
8 of life and biologic activity measures are certainly
9 potentially helpful in getting a sense about
10 mechanisms of action and biological plausibility of
11 efficacy.
12 But in the context of having such an
13 extremely informative study in 107, in a relative
14 sense they don't provide very much more insight.
15 Hence I would say probably are largely irrelevant in
16 the context of what we have already learned from 107.
17 Would you be better off without them? No.
18 The sponsor certainly might have had a stronger case
19 in the sense that 106 and 110 are negative. One, oh,
20 seven is also negative on six minute walk, but is
21 positive on quality of life and signs and symptoms.
22 So, in essence, overall I would argue that
23 measures of biologic activity are of relevance in
24 establishing plausibility, but don't provide direct
25 evidence about that, and the information on quality of

1 life was actually in those two studies, was fairly
2 negative.
3 ACTING CHAIRMAN BORER: Steve.
4 DR. NISSEN: A very brief comment. I
5 agree with everything Tom said, except the hemodynamic
6 data. I think it's important for us to all remember
7 the paradox of inotropic agents, which make
8 hemodynamics better and probably adversely affect
9 survival, I think.
10 So I don't see a lot of signal. If one
11 shows me an acute hemodynamic effect of a drug, it
12 doesn't really tell me very much about whether it's
13 going to be useful in chronic heart failure, and so
14 they're noncontributory from my perspective.
15 I think they help the sponsor more to
16 understand whether there is some additive hemodynamic
17 effect over ACE inhibitors, but other than that, I
18 think they're not really very helpful for this
19 application.
20 ACTING CHAIRMAN BORER: Alan, did you have
21 a comment? No.
22 Ray.
23 DR. LIPICKY: Well, in part it might be
24 worth hearing a comment or two if you think it's worth
25 commenting on. Those other studies did have some

1 aspect of do patients feel better, and it wasn't
2 striking that there was or that they found anybody
3 feeling better, and that is sort of not the case in
4 Val-HeFT.
5 It rather strikingly seemed to make people
6 feel better even when they were on ACE inhibitors. So
7 part of the question is does that detract from how
8 you're going to interpret what you see in Val-HeFT.
9 DR. COHN: May I remind Ray?
10 ACTING CHAIRMAN BORER: Yes.
11 DR. COHN: What we found is there's
12 benefit for the long term. These other studies were
13 before any of the curves began to separate. So we
14 kept people from feeling worse. We didn't make them
15 feel better. That's why I made the --
16 DR. LIPICKY: Okay, okay.
17 ACTING CHAIRMAN BORER: Actually I was
18 going to remind you of that, too.
19 DR. LIPICKY: You were?
20 (Laughter.)
21 ACTING CHAIRMAN BORER: You know, for me,
22 and anybody on the committee, chime in and disagree,
23 I don't find the lack of clinical efficacy in these
24 trials to be particularly compelling against because
25 there were small trials over a short period of time,

1 and we have this overwhelming data set that is
2 compelling in the other direction.
3 So it's not a big negative for me. Is it
4 for anyone else? No.
5 Okay. Number 3, consider the components
6 of the morbidity and mortality endpoint of Val-HeFT,
7 and we have this nice table here. What role do each
8 of the components have in the case for approval? And
9 how do we reconcile the large effects on
10 hospitalization with post hoc analyses that show
11 little or no effect on certain of the subcomponents?
12 Tom, why don't you just go ahead?
13 DR. FLEMING: All right. This is
14 certainly an important question. The first part, what
15 role do the components play, my sense in interpreting
16 the components is what is apparent as you look at
17 these four components. The results are really driven
18 by all cause mortality and CHF hospitalizations.
19 And the sponsor's presentation today
20 certainly did focus appropriately on those two
21 elements. They're complementary. All cause
22 mortality, obviously a critically important endpoint
23 to these patients, but certainly CHF hospitalization
24 is a separate measure that is going beyond mortality
25 looking at issues of quality of life, although as was

1 discussed by the committee, one would have possibly
2 hoped that through affecting CHF hospitalization that
3 might have led you to anticipate a mortality benefit
4 as well.
5 But I look at them as largely
6 complementary and very important elements, and those
7 two elements are the two for which we have very
8 substantial information about benefit.
9 Ray, if you could put up the first of
10 those two slides.
11 The 3.2 though gets into the question
12 about reconciling evidence for a favorable result on
13 CHF hospitalization, but with little or no effect on
14 all cause hospitalization.
15 And a slide that I had generated, and
16 actually I think these results are similar to what the
17 sponsor had presented in their attempt to clarify this
18 issue as well; what we're looking at here on the top
19 of this slide are events, are basically numbers of
20 people in the trial with events where, of course, we
21 have about 2,500 per arm, and we know that the death
22 rate is about 20 percent of the patients in each of
23 these two arms had died, where there is a two percent
24 increase in deaths.
25 But we see if we -- and it is problematic

1 to censor the deaths, but that's the approach here in
2 analyzing what I underlined in green, which was the
3 result that was referred to as the favorable result in
4 this Question 3.2, and it certainly is.
5 I think we would all accept the most
6 important positive signal in this study is this 27
7 percent estimated reduction in CHF hospitalizations,
8 and these together provide the second primary
9 endpoint, the 13 percent reduction in morbid events.
10 Now, the FDA asks the sponsor to provide
11 in addition to that the numbers of patients that had
12 hospitalization for any cause or death, and when you
13 look at this data, you see no reduction, and so the
14 paradox or the uncertainty here is why is it that we
15 have no reduction in the numbers of patients that have
16 death or all cause hospitalization when we're seeing
17 a reduction from about 18 and a half percent to 14
18 percent of patients that would have CHF
19 hospitalization? Does that mean that, in essence,
20 there is an increase in non-CHF hospitalization?
21 Well, I think to really more appropriately
22 address that and to get better insight into that, we
23 have to look in addition to this analysis, which is
24 the numbers of people with an event; we need to look
25 at the numbers of events overall.

1 And I think a very important -- and these
2 data, by the way, are in the FDA briefing document on
3 pages 96 to 99. What's relevant here is that whereas
4 there are about 1,365, 1,398 patients with at least a
5 hospitalization or death event, the actual number of
6 hospitalizations is two to two and a half fold as
7 high. This is the total number of hospitalizations
8 that are recorded over the duration of follow-up,
9 2,056 versus 3,106, which separate into those
10 hospitalizations that are CHF and those that are non-
11 CHF.
12 And in essence, what you see here is not
13 that there's an increase in non-CHF hospitalizations,
14 but there is this overall decrease of about 260 CHF
15 hospitalizations that shows up in all cause.
16 Ray, I would say, in essence, what's
17 happening here is what's giving the impression that
18 there isn't a reduction in all cause events, is that
19 basically we've having multiple repeated
20 hospitalizations of both types occurring to many of
21 these patients over the two year period of follow-up.
22 So I found these analyses that looked at
23 the total numbers of events to be very informative,
24 and in fact, the all cause hospitalization days data,
25 I think, is very consistent with all cause

1 hospitalization.

2 You've got roughly an eight percent

3 reduction in the number of all cause hospitalizations.

4 You've got about a ten percent reduction in the number

5 of days.

6 What I'd like to do is in a minute go to

7 another slide that basically then puts into context

8 what the survival data, all cause hospitalization and

9 all cause hospitalization days would look like for a

10 hypothetical 100 people.

11 Ray, could you put that other slide up to

12 basically finish this response to this part of

13 Question 3.2?

14 If we looked at a typical 100 people then

15 based on data from the Val-HeFT trial, where that data

16 provided approximately two years' follow-up, what we

17 would have in 100 typical people with about two years'

18 follow-up is about 20 deaths on placebo and about 20

19 deaths on valsartan. There would be no change in the

20 numbers of deaths.

21 Essentially, you would reduce for these

22 100 people the total number of all cause

23 hospitalizations from 124 to 114. That's entirely --

24 those ten are entirely CHF hospitalizations.

25 So the total number of non-CHF

1 hospitalizations would be 77 in both groups, but would
2 be reduced by ten the number of CHF hospitalizations.
3 And correspondingly, with this ten percent
4 reduction we would reduce by ten percent the number of
5 hospitalization days.
6 So, in essence, what we're looking at here
7 in a typical 100 people that would receive valsartan
8 versus 100 that would receive placebo, no difference
9 in deaths; no difference in non-CHF hospitalizations;
10 but ten less CHF hospitalizations per 100 people,
11 translating into about a day less.
12 So the number of days alive and non-
13 hospitalized is about 690 per arm, and the number of
14 hospital days is reduced by about a day. So one way
15 of looking at all of these data is that these results
16 suggest no effect on mortality, an average of one-
17 tenth of a CHF hospitalization per patient eliminated.
18 That translates into one less hospitalization day.
19 And in essence, then that really addresses
20 all three of these elements of 3.2.
21 ACTING CHAIRMAN BORER: Does anybody have
22 any additional comment about this question? Steve.
23 DR. NISSEN: Yeah. Well, I also want to
24 complement the sponsor on it. I think this is an
25 incredibly important and informative study, and if I

1 seemed nitpicky about it, it's because that's our job,
2 and I'm going to nitpick a little bit more here before
3 we finish and say that, you know, while these
4 differences are impressive, I would have been happier
5 if the adjudication had been done differently. I
6 think it would have made my confidence of the data a
7 lot higher in terms of looking at these differences
8 because the differences, as pointed out by Tom's
9 analysis, are relatively modest.
10 I can't accept that coming into the
11 hospital at nine o'clock in the morning, getting
12 furosemide intravenously all day long and going home
13 that evening is not an event, but doing the same thing
14 at nine o'clock at night and being overnight is.
15 Now, the excuse that the data on the time
16 were not available is a flaw in the design. It's easy
17 to put in the case report form. What time did the
18 patient get admitted to the hospital and what time do
19 they get discharged? You can collect that data.
20 And, you know, suggesting that the time of
21 day at which you get admitted would make such a big
22 difference on whether it was counted as an event or
23 not is a weakness that could have been overcome by
24 more meticulous, you know, design.
25 And, secondly, I think that to me

1 independent adjudication means the sponsor is not
2 present. In many, almost all of the trials I've been
3 involved with that's how it's been done, and I think
4 there's good reasons for that because if the committee
5 is doing the selection of the cases along with an
6 independent, you know, group or CRO, whatever, it
7 protects the study.
8 I think that it didn't make a difference
9 here. Please don't get me wrong, but I think it helps
10 our confidence more if it looks like the adjudication
11 for a trial where these events were the endpoint of
12 the trial, where you're spending I don't know how many
13 tens of millions of dollars on a trial. It's worth a
14 little extra effort to adjudicate these endpoints in
15 the cleanest fashion possible and trying to understand
16 that right up front.
17 Having said all of that, you know, I do
18 think that Tom's comments are really along my line.
19 I agree with his comments.
20 ACTING CHAIRMAN BORER: Ray.
21 DR. LIPICKY: I guess I'm setting myself
22 up to be hollered at, but the way you presented the
23 results, Tom, I was more impressed before. A tenth of
24 a hospitalization? Is that worth adding the seventh
25 drug to a treatment regime, et cetera, et cetera?

1 You made it seem like the effect is very
2 small.
3 ACTING CHAIRMAN BORER: That's in 100
4 patients.
5 DR. LIPICKY: A tenth of a hospitalization
6 per patient.
7 DR. FLEMING: Yeah, basically if we put it
8 in the context of per 100 patients followed over two
9 years, then in those 100 patients treated, you would
10 prevent ten hospitalizations. That is a tenth of a
11 hospitalization per patient, but that's basically ten
12 hospitalizations prevented for 100 patients treated
13 and followed for two years.
14 DR. LIPICKY: So you do think it's small?
15 DR. FLEMING: Well, that's what we --
16 DR. LIPICKY: You're not going to holler
17 at me?
18 DR. FLEMING: I mean, my assumption is
19 we'll be coming back to that specific discussion later
20 on.
21 DR. LIPICKY: Okay, fine.
22 DR. FLEMING: One of the issues that you
23 were raising here was specifically how is it that we
24 could see reductions in the number of patients
25 experiencing CHF hospitalizations and not see any

1 reduction in the total number of all cause
2 hospitalizations.
3 And the answer for that really reflects
4 the fact that these patients are being followed over
5 a time frame where there are really repeated events
6 occurring, and as those repeated events occur, the
7 numbers of people then that have at least one event
8 becomes less informative about what the overall effect
9 is.
10 But you think step back and look at the
11 analyses that I was showing at the bottom of that
12 first transparency. Then you do see that, in fact,
13 even though the numbers of patients that have at least
14 one hospitalization are the same, there really is not
15 a negative effect in these data on non-CHF
16 hospitalizations.
17 But the overall level of effect is,
18 therefore, none. In the typical hundred patients, I
19 don't have that slide in front of me now, but I think
20 it was 77 versus 77 non-CHF hospitalizations and CHF
21 hospitalizations were what was it? Thirty-seven
22 against 47?
23 DR. LIPICKY: That's okay. So you will
24 make a value judgment later. So we --
25 DR. FLEMING: I definitely think we

1 should.

2 DR. NISSEN: Just let me holler at you a

3 little bit and say that I would agree with you if it

4 weren't for the fact that the study design was adding

5 this agent to what was already very good state-of-the-

6 art therapy, and so this degree of reduction on top of

7 people who were very well treated is much more

8 impressive than it would have been in another setting.

9 DR. LIPICKY: Agreed, but in a public

10 health sense it's not too important.

11 DR. NISSEN: Again, I wouldn't necessarily

12 agree with you about that. I mean, if you have to

13 treat ten patients to prevent one hospitalization,

14 hospitalizations use a lot of resources. They cost a

15 lot, and they're not very pleasant for patients that

16 undergo them.

17 I don't have a problem with giving a drug

18 to ten people to prevent one of them from being

19 hospitalized. That to me is a fairly impressive

20 effect in this setting.

21 DR. LINDENFELD: Don't you think, Steve,

22 though that we should consider it 20? Because we

23 usually think about number needed to treat per year.

24 So this is ten for two years. So that would mean

25 you'd have to treat 20 to save one hospitalization.

1 DR. NISSEN: JoAnn, and this is in the
2 same range --
3 DR. LINDENFELD: So that makes it a more
4 modest --
5 ACTING CHAIRMAN BORER: Can I just add?
6 Let's hold this discussion, if I may, because --
7 DR. LIPICKY: I withdraw the question.
8 ACTING CHAIRMAN BORER: -- you know, the
9 question we're actually going to have to answer at the
10 end of the day will incorporate elements of all of
11 this, and we can get to it.
12 And with that in mind, can I ask, Ray,
13 that we be allowed to skip number four? Because
14 unless, Tom, you have something very much to say about
15 it, because it's sort of a speculative value judgment
16 that we're going to get to.
17 DR. LIPICKY: No, no, no.
18 ACTING CHAIRMAN BORER: I mean, we're
19 going to get to it.
20 DR. LIPICKY: No. It gets at the very
21 thing that Lloyd got up to talk about.
22 ACTING CHAIRMAN BORER: Well --
23 DR. LIPICKY: What is the level of
24 significance you want from a single trial before you
25 start paying attention to it if you only deal with the

1 primary endpoint?

2 DR. FLEMING: I think I can comment.

3 DR. LIPICKY: Or endpoints.

4 ACTING CHAIRMAN BORER: Okay.

5 DR. LIPICKY: And then are you going to

6 modify that based on what you see later?

7 ACTING CHAIRMAN BORER: I withdraw my

8 request, Ray, and I'm going to ask Tom to give the

9 definitive answer.

10 DR. FLEMING: Well, I think I can give at

11 least a brief comment in response to this, and I think

12 it does -- it really is. The way this is phrased is

13 very specifically asking us to just look at the co-

14 primary endpoints, not look at secondary. The

15 questions will lead us then through five and six to

16 bring in secondary endpoints and how does that

17 influence our perspective?

18 As I see it, there are in Question 4,

19 there are two aspects to address in this question.

20 Basically what it's asking us is if we focus on the

21 primary endpoints, how strong do these results have to

22 be for us to view that these are significant or

23 established benefits of clinical importance, and I

24 think there are two elements.

25 There's statistical significance below the

1 line, and there's clinical significance above the
2 line, and this trial is a very important, very good
3 trial. It's 5,000 patients. It's a trial that was
4 adequately powered for mortality, which was a negative
5 outcome, and by all likelihood, I was probing this and
6 didn't really get a clear answer, but in all
7 likelihood, it's more than adequately powered to
8 address the other primary endpoint of morbidity, given
9 that there are a lot more morbidity events than
10 mortality events.
11 That being the case, it's a study with
12 considerable potential to achieve a very strong level
13 of significance if there's a strong signal of effect.
14 Traditionally, it's only a guideline, but
15 statistical procedures are useful as a guide. We have
16 considered results at the 025 level, two sided, as the
17 strength of evidence that we would need to see to call
18 a study positive. In this trial with co-primary
19 endpoints and adjusting for multiple testing, that
20 two-sided p value guide is not 05, but 02.
21 If we looked at this as a trial that
22 provided, in essence, comparable strength of evidence
23 to two independent studies, each of which would be
24 positive, that's where the 00125 has arisen, and
25 technically here I'd remind you it's not .00125 in

1 this trial,b ut that divided by two or even more than
2 two, because there was interim monitoring and there
3 were two primary endpoints. So --
4 DR. FISHER: Could I say --
5 DR. FLEMING: -- essentially --
6 essentially what we are dealing with here is a trial
7 from a strength of evidence if we focus only on, as
8 we're asked to in this question, the primary endpoints
9 that would meet the standard for what would be called
10 a positive study on the morbidity endpoint.
11 But it doesn't really come close to what
12 we would consider as essentially comparable to the
13 evidence of two independent positive studies each of
14 which just exactly hit strength of evidence that we
15 would need individually.
16 The issue above the line of clinical
17 relevance is certainly also very important. What
18 we're estimating is a 13 percent reduction in the
19 morbidity events, and I think that is an issue that we
20 need to revisit, as we've said, toward the end in
21 talking about what level of effect is, in fact,
22 clinically important.
23 ACTING CHAIRMAN BORER: Tom, Lloyd raised
24 a question. In general we wouldn't have more comments
25 here, but specifically about your calculations.

1 DR. FISHER: I wanted to give a point of
2 information. This is just a numerical fact according
3 to -- the number .1 is wrong. There's actually a gain
4 of one day per patient per year.
5 So in other words, if you're treating
6 somebody for a year on the average, that person is
7 prevented for a day of hospitalization.
8 Of course, as it turns out, it's very
9 skewed. Some people are not hospitalized at all, and
10 some more. So but on the average, each person each
11 year gains a day.
12 DR. LIPICKY: That makes it a big number,
13 does it? No, you don't have to answer that.
14 DR. FISHER: Well, no.
15 (Laughter.)
16 DR. FISHER: I've been in the hospital,
17 and all I can tell you it wasn't a particularly
18 wonderful experience given the -- for me it would be
19 worth avoiding it, but --
20 DR. LIPICKY: Yeah, I agree. I don't
21 disagree.
22 ACTING CHAIRMAN BORER: Okay. Ray, can we
23 postpone further elaboration on four until we move a
24 little further?
25 DR. LIPICKY: Yes.

1 ACTING CHAIRMAN BORER: Thank you.

2 Okay.

3 DR. LIPICKY: You're welcome.

4 ACTING CHAIRMAN BORER: Let's move on to

5 number five. Consider other endpoints that were not

6 individual components of the morbidity/mortality

7 primary endpoint of Val-HeFT, and we have a table here

8 with a number of them with some p values.

9 What role do each of these secondary

10 endpoints have in the case for approval?

11 Tom, why don't you go through that?

12 DR. FLEMING: Okay. In any trial, it

13 certainly is very important to focus, first and

14 foremost, on the primary endpoints, in this case two

15 primary endpoints, mortality and the morbidity

16 hospitalization/mortality endpoints.

17 But in any trial it's also clearly

18 important to focus beyond or to take into account, as

19 well, the supported information. It becomes more

20 subjective in interpreting those data. I tend to put

21 less emphasis on p values and more emphasis on what is

22 the magnitude of effect and how reliably is it

23 estimated.

24 It is certainly relevant though to be

25 considering how the safety profile, as well as

1 secondary quality of life measures influence one's
2 overall perspective of benefit to risk. What we have
3 here, as has been summarized in the question, there
4 are an array of secondary measures.
5 In particular, I might focus on the
6 overall signs and symptoms results, as well as the
7 Minnesota living with heart failure questionnaire
8 results, and these data are presented in the sponsor's
9 presentation on pages 51 and 52.
10 There is important positive reinforcement
11 with these results. It is important though or
12 relevant, at least as I look at these results, to note
13 in the signs and symptoms that what we're seeing is on
14 the order of a one to three percent increase in the
15 number of patients that have improvement in fatigue,
16 dyspnea, rales, et cetera, and one to three percent
17 decrease in the numbers who have worsening, which in
18 these sample sizes are showing up as statistically
19 significant.
20 In the Minnesota living with heart failure
21 where the overall scale at baseline was about 32,
22 we're seeing a relative benefit of about one and a
23 half points, preventing a one and a half point
24 decline, in essence, and in these sample sizes, these
25 results are showing up as significant at the 01 to 001

1 level in many cases.

2 The key question that I would throw out

3 though is more than from a statistical perspective,

4 from a clinical perspective. How important is this?

5 It is a benefit. It is of some importance, but how

6 important, for example is a change of one and a half

7 points in the Minnesota living with heart failure

8 questionnaire?

9 ACTING CHAIRMAN BORER: Steve?

10 DR. NISSEN: Yeah, this actually has a

11 fair amount of weight with me, and again, when you

12 only have one really good trial, big trial to look at

13 is what we really have here, and I would point out

14 something to you, Tom. You know, for those of us who

15 see patients with heart failure, it's not a pleasant

16 disease. Waking up in the middle of the night with

17 paroxysmal nocturnal dyspnea is not any fun, and the

18 fact that, you know, highly significant differences,

19 particularly the symptoms here of heart failure,

20 because ultimately making these folks feel better is

21 important.

22 I know, Ray, you've emphasized in a lot of

23 development programs, you know, the feel good aspects

24 of this, and this is very supportive, and I would have

25 been much less enthusiastic here if these things had

1 all been neutral.

2 But you know, dyspnea on effort, you know,
3 walking out to get your mail and doing the things you
4 do, if you have less shortness of breath doing that,
5 that's a good thing.

6 And so to me it's very supportive and it's
7 very important, and I'm glad it was here and I'm glad
8 it was done in this trial.

9 DR. FLEMING: Steve, let me be specific
10 though. The issue that I'm trying to raise is not
11 whether these symptoms are important. The question
12 is: how much of an influence on these symptoms does
13 one have to generate in order to say this is an
14 important effect?

15 So if we look at paroxysmal nocturnal
16 dyspnea, whereas in the intervention arm 6.6 percent
17 improve, in the placebo 5.7 percent improve. Are you
18 impressed that there is that extra .9 percent
19 improvement?

20 DR. NISSEN: I am impressed.

21 DR. LIPICKY: Well, let me stake out a
22 position so that you can argue with it.

23 DR. NISSEN: Okay.

24 DR. LIPICKY: Okay? With respect to the
25 primary endpoint, this is one trial that has some

1 other data that doesn't really tell you much. I would
2 say the primary endpoint had to have a p value of
3 .00125, and if it didn't, I wouldn't want to look much
4 farther.
5 But in fact, you say, "Well, I'm going to
6 look a little farther." Okay, and so you look at the
7 secondary endpoints, and as Tom said, you don't know
8 how to evaluate the strength of evidence there, but
9 you have sort of magnitude effects to look at.
10 This is a five percent change, ten percent
11 change, 20 percent change. So does that mean then
12 that you're going to say based on the secondary
13 endpoints I modify my stand? I'm satisfied with the
14 p of .01 for the primaries because this really means
15 something to me. Then we'd have to start talking
16 about, well, when do you modify the way in which you
17 make your first decision on the basis of looking at
18 other data when you don't have much ability to be able
19 to decide whether the other data is real or not in any
20 usual sense.
21 That's what's going on here, and I
22 contracted it and took extreme positions so that you'd
23 recognize that.
24 ACTING CHAIRMAN BORER: Paul, do you have
25 any thoughts about this that you want to share, the

1 importance of these secondary endpoints?

2 DR. ARMSTRONG: I am impressed by their

3 consistency, and so I think in that -- but also the

4 fact that I don't put as much weight on them

5 individually as a package in terms of clinical signs

6 and symptoms and their concordance with the other

7 measures. So to the extent that they support that, I

8 think they're useful.

9 DR. FLEMING: Paul, this is a really tough

10 question to ask because there's obviously a lot of

11 subjectivity to this, but is there any literature? We

12 talk about the Minnesota living with heart failure

13 questionnaire as being validated. Is there a

14 literature that says essentially something about

15 magnitude of change on that scale for it really to be

16 clinically relevant?

17 I guess what I'm really getting at is a

18 one and a half point change, something that clinically

19 is profound, moderate, but important, really modest,

20 or close to irrelevant.

21 DR. ARMSTRONG: Well, as you would know,

22 a one and a half point change on a denominator of six

23 in a common problem might be quite relevant. And

24 rales and third heart sounds track morbidity and

25 mortality pretty well in heart failure.

1 DR. FLEMING: Well, I'm looking
2 specifically at the Minnesota where the baseline
3 average was 32, and based on having that baseline
4 average of 32, which we were informed basically was
5 moderate in the range, what do we know about a one and
6 a half point change and how important that is
7 clinically?
8 DR. COHN: Well, I guess I should probably
9 address that because this is our form.
10 DR. FLEMING: Although to be candid here,
11 this is -- I'd really like to get an opinion
12 independent of the sponsor here, Jay, if you would.
13 I would prefer not to get -- I think --
14 DR. COHN: I mean, I can give you the
15 background on the form.
16 DR. FLEMING: But at this point --
17 DR. COHN: Okay.
18 DR. FLEMING: -- I would prefer to get my
19 colleagues' opinions on the committee.
20 DR. HIRSCH: Maybe we should all speak up.
21 I don't think we know the answer to that question. I
22 think it's just another signal like the change in
23 signs and symptoms that can't be quantified or
24 qualified even though there isn't development
25 information.

1 Going down the panel, as we always do?

2 DR. LINDENFELD: I agree it's a signal,

3 but I think it's very much like the signs and

4 symptoms. It's a modest --

5 DR. HIRSCH: Okay.

6 ACTING CHAIRMAN BORER: I must say for

7 myself I'm very impressed with the consistency of the

8 data over so many areas that might be evaluated, and

9 personally I think that tools for measuring

10 symptomatic benefit are inherently -- inherently

11 provide information that's extraordinarily imprecise,

12 and the result is that you should see anything at all

13 is impressive to me, whether it's one point, two

14 points, or three points on a scale that's

15 fundamentally subjectively defined.

16 We see many trials with many tools, not

17 only the Minnesota scale, but New York Heart

18 Association functional class for a lot of

19 cardiovascular problems. You know, it's often very

20 difficult to see anything despite overall benefit as

21 measured by certain objective endpoints.

22 So I'm impressed that there's anything

23 positive here with the Minnesota scale.

24 DR. FLEMING: But, Jeff, you're saying

25 what impresses you is that in many other trials of

1 other agents there are no effects. So the fact that
2 there is anything here is impressive, and yet I'd say,
3 "Well, look at other endpoints. Look at mortality."
4 ACTING CHAIRMAN BORER: Right.
5 DR. FLEMING: We have other agents that
6 show big effect on mortality. There's no effect here.
7 ACTING CHAIRMAN BORER: That's true, but
8 what I see -- I don't want to jump ahead here, but
9 what I see here is a drug that in this population
10 overall didn't have much of an effect on duration of
11 life, but it did seem to have an effect on how
12 patients felt in terms of the various measures that
13 were made.
14 If you look at the co-primary endpoint,
15 which is one of the feel good endpoints, and you look
16 at collateral data that might support that that
17 endpoint should be accepted as meaningful, when I see
18 the Minnesota quality of life scale coming out
19 positive, that makes me more confident that the co-
20 primary endpoint is a meaningful one, that the result
21 on the co-primary endpoint is a meaningful one.
22 If it were the only positive and all of
23 these others sort of fell out 50-50, I'd be much less
24 impressed, but that as a component of 12 or 15 other
25 parameters that were looked at here, all coming out

1 the same way, impresses me a great deal.

2 DR. LIPICKY: Well, but --

3 ACTING CHAIRMAN BORER: Knowing as I do

4 how difficult it is to get a history of symptoms that

5 is positive when you apply a drug. So, you know, I

6 think the package has to be taken together. This is

7 one component of the package, and it wouldn't matter

8 to me if it was one point or five points. If it were

9 the only component of the package that went the right

10 way, I'd be concerned.

11 But if it goes the right way and it's one

12 point and the other data are consistent with it, I

13 find it impressive.

14 DR. LIPICKY: Jeff, are you talking about

15 the point estimates going in the right way or how do

16 you know that that's real?

17 ACTING CHAIRMAN BORER: Well, I don't know

18 that it's real, but I know --

19 DR. LIPICKY: Are you looking at the p

20 values here?

21 ACTING CHAIRMAN BORER: I know that it's

22 consistent --

23 DR. LIPICKY: How can you interpret those

24 p values? Tell me how you interpret. What does a p

25 of .004 mean?

1 ACTING CHAIRMAN BORER: I interpret it as
2 indicating to me that the result was consistent across
3 the population. That's the only interpretation I make
4 of it.
5 DR. LIPICKY: But on the basis of the
6 point estimate or the p value?
7 ACTING CHAIRMAN BORER: No, on the base of
8 the p value I say that the result for that point
9 estimate, the result that that is the point estimate
10 of is consistent through the population.
11 DR. LIPICKY: I see.
12 ACTING CHAIRMAN BORER: And now we have
13 consistent through the population for many, many point
14 estimates. The magnitude of the point estimate really
15 doesn't mean all that much to me.
16 DR. FLEMING: But here, Jeff, the
17 challenge is really getting a sense of whether the
18 changes that we see in dyspnea at rest and dyspnea on
19 effort and fatigues, all of these measures showing two
20 or three percent more people showing improvement. Are
21 these -- I mean, we keep making it a point. It's
22 really impressive that there are all of these
23 endpoints. Is it maybe very much the same two or
24 three people that are showing this level of
25 improvement on measures that are highly correlated

1 with each other?

2 ACTING CHAIRMAN BORER: Yeah, it may well

3 be. It may well be.

4 DR. FLEMING: So it doesn't take away from

5 the argument. It's favorable that we showed an effect

6 rather than not showing an effect. I'm not debating

7 that, although I'm worried about how much of an effect

8 it is, but I guess I'm concerned about the conclusion

9 that there's a page here of results, and most of them

10 are significant, and this is overwhelmingly

11 strengthening the conclusions because they're all

12 significant when many of them must be heavily

13 correlated.

14 ACTING CHAIRMAN BORER: Yeah, I think they

15 are, but even with relatively heavily correlated

16 parameters, when you look at a heart failure database,

17 they generally don't all go the same way, you know.

18 DR. ARMSTRONG: Tom, maybe it would be

19 helpful to say that the New York heart class, which is

20 common to many other studies, does show a 2.4 percent

21 improvement, and I think we could collect all of the

22 symptoms in the New York heart class and say there's

23 not a bad bed rock based on the other studies that

24 looks like it moves, and then we could look at the

25 signs, edema, the third sound, and others, and say

1 there's probably two clusters in this data. One is
2 symptoms and the other is signs, and they go in the
3 right direction.
4 And for me as a clinician, that seems to
5 make sense.
6 DR. LIPICKY: Well, a third heart sound
7 doesn't do that.
8 ACTING CHAIRMAN BORER: Yeah, the other
9 point --
10 DR. LIPICKY: Orthotomy (phonetic), it
11 doesn't do that.
12 DR. ARMSTRONG: That's the toughest one to
13 get.
14 ACTING CHAIRMAN BORER: Before you speak,
15 Steve, the other point here is a point that you made,
16 that you, Steve, made just a few minutes ago. You
17 know, when I try to interpret these data, one of the
18 confounders in the interpretation is the fact that
19 there were so many other drugs on board at the outset
20 of therapy. So that my expectations may be less than
21 they would be if those confounding drugs weren't
22 present.
23 Now, it's difficult to make the
24 interpretation of what the confounding drug -- of how
25 the confounding drugs affect the data. We don't know.

1 The studies weren't designed to tell us.

2 If you go back then and look at the sub-

3 analyses that were done, which I don't want to make

4 too much of yet because we're going to get back to

5 them later in a way that perhaps is a little different

6 from the way that the sponsor presented them, but if

7 you do look at them, if you look at the sub-analyses

8 and you look at the people who weren't on ACE

9 inhibitors and weren't on beta blockers, why, my

10 goodness, the results come out the way I would have

11 expected them to if this is a drug that works and does

12 good things.

13 So, you know, when you take the totality

14 of the little pieces, they seem all to point in a

15 reasonable direction if one were to conclude that this

16 drug has a clinical benefit in terms of relief of

17 symptoms and prevention of hospitalizations.

18 Steve?

19 DR. NISSEN: Yeah, two quick points that

20 may make Tom a little more comfortable. To really

21 look at this fairly, you have to kind of look at this

22 to some extent as a risk ration. Not everybody has

23 PND, and so you know, if you reduce from seven percent

24 incidence of PND to five percent incidence, then as a

25 risk ratio, you know, that's a pretty big decline.

1 Looking at it in terms of absolute numbers
2 for any individual marker is really not fair to that
3 marker.
4 And the second point I wanted to make is
5 that what to me really struck my eye when I reviewed
6 this is that these are not all markers that are
7 markers of symptoms. Some are markers of symptoms.
8 Some, like left ventricular diastolic diameter, are
9 markers of anatomy suggesting that there's effect on
10 the anatomic progression of ventricular dilation or
11 ejection fraction is another measure like that.
12 And some were measures of physiology, like
13 jugular venous distension and rales. And so to me it
14 is comforting when I see symptomatic changes,
15 physiological changes and anatomic changes all going
16 in the same direction, and so it's just reinforcing.
17 And so, Ray, it does have an impact. Now,
18 how big an impact should --
19 DR. LIPICKY: Well, that's what we wanted
20 to find out, and since we failed in answering Question
21 4 --
22 ACTING CHAIRMAN BORER: Yeah.
23 DR. LIPICKY: -- because you were supposed
24 to name a number, will you go back to four and name a
25 number? That is, you would expect that you would act

1 favorably just based on the primary endpoint on --

2 ACTING CHAIRMAN BORER: And you want a p

3 value or a --

4 DR. LIPICKY: -- something that was in the

5 first --

6 ACTING CHAIRMAN BORER: -- hazard ratio or

7 both?

8 DR. LIPICKY: -- block, second block,

9 third block or fourth block of that line. It's a

10 visual analogue scale. You can draw the line anywhere

11 you want to.

12 DR. HIRSCH: The fact that we're spending

13 so much time trying to avoid the question, I think,

14 gives you part of the answer. Bill you want to try?

15 DR. LIPICKY: Well, just, you know,

16 there's one, two, three, four -- four possible places

17 you can put the line. Pick one.

18 ACTING CHAIRMAN BORER: Alan, would you

19 or, Tom, go ahead.

20 DR. LIPICKY: Let's number them from left

21 to right, one, two, three, four.

22 DR. FISHER: Can I make one quick

23 technical comment?

24 Jeff is right. Hazard ratio is a

25 biological parameter of the population. P value

1 depends upon the study design and sample size, and so
2 you might want to separate your lines. I mean this is
3 the values that may go together with this study, but
4 there's no necessary linkage between the two.
5 DR. LIPICKY: Yeah, that's true, but it
6 makes it -- we can't answer even this question, let
7 alone making it a little more complicated.
8 DR. HIRSCH: And these values pertain to
9 populations, and we're talking about individuals here
10 at risk with quality of life questionnaires. So it
11 really is a mental segue I'm not really comfortable
12 going down.
13 DR. LIPICKY: So all we want to know, and
14 it's just name and number, one, two, three, four
15 starting from the left --
16 DR. FLEMING: Well, there are two issues
17 here, and in fact, --
18 DR. LIPICKY: Well, lower --
19 DR. FLEMING: -- Ray, I tried to -- I
20 tried to answer this --
21 DR. LIPICKY: Yeah, you're right.
22 DR. FLEMING: -- the first time through
23 when we got to Question 4, and I stated there are two
24 issues. There's the below the line issue, which is
25 strength of evidence, and there is the above the line

1 issue, which is magnitude of effect.

2 DR. LIPICKY: Fine, fine.

3 DR. FLEMING: An they are both --

4 DR. LIPICKY: Fine.

5 DR. FLEMING: -- important issues.

6 DR. LIPICKY: So then if --

7 DR. FLEMING: The below the line issue, if

8 we would follow what would be a traditional guide, and

9 the critical word there is "guide" --

10 DR. LIPICKY: Right.

11 DR. FLEMING: -- any interpretation of a

12 study requires careful consideration of totality of

13 results, but should be heavily influenced by strength

14 of evidence on the primary endpoint.

15 A tradition here would be to call this a

16 single positive study or the evidence consistent with

17 that, we would typically be using two sided .05, but

18 remembering here that it's really two sided about .02,

19 reflecting multiple testing and multiple primary

20 endpoints.

21 Correspondingly, if you said, "Gee, what

22 would it take in statistical strength of evidence to

23 equate with two trials, each of which would hit the

24 standard that I just mentioned?" it wouldn't in this

25 case be .00125. It would be about less than half that

1 because .00125 doesn't adjust for the two primary
2 endpoints.
3 DR. LIPICKY: So it would be --
4 DR. FLEMING: It would be about .0005, and
5 so --
6 DR. LIPICKY: So it would be line segment
7 one.
8 DR. FLEMING: so the simple answer to your
9 question purely from a statistical perspective is that
10 this study does hit the strength of evidence just by
11 a bit, not by a lot, standard for being called a
12 positive trial, but really doesn't come close to what
13 we would have typically stated was equivalent to the
14 strength of evidence that you would have from two such
15 positive trials.
16 DR. LIPICKY: Right. Okay.
17 DR. FLEMING: Now, the clinical issues
18 are --
19 DR. LIPICKY: So that's a very clear
20 answer, right? So --
21 DR. FLEMING: So now you want a number.
22 DR. LIPICKY: Well, if anyone disagrees
23 with that answer, that would be important to say, and
24 if no one wants to disagree, that's fine, and then we
25 can go on because that same question comes up. Now

1 you've got secondary endpoints. What are you going to
2 do?
3 DR. FLEMING: Okay.
4 DR. LIPICKY: Okay?
5 DR. FLEMING: Okay.
6 DR. LIPICKY: But that will give us a
7 feeling for what you think. Otherwise you're leaving
8 us up in the air.
9 ACTING CHAIRMAN BORER: Can I just add one
10 comment to Tom's comment? You've asked about the
11 hazard ratio, as well.
12 DR. LIPICKY: Yes.
13 ACTING CHAIRMAN BORER: Which is the
14 above-the-line part that Tom spoke about before, and
15 I would say that it would be very difficult for me to
16 provide a hazard ratio which is appropriate except in
17 the context of this trial not to be extrapolated
18 elsewhere because of the issues that we've already
19 discussed --
20 DR. LIPICKY: Fine.
21 ACTING CHAIRMAN BORER: -- confounders
22 that we can't interpret.
23 If you want a number, I'll tell you a
24 number.
25 DR. LIPICKY: No, that's fine. I think

1 you can ignore, I'm sorry to say, what Lloyd said
2 because these hazard ratios were calculated on the
3 basis of this data. So you could look at this sort of
4 as the same scale, and what that was really asking for
5 was do you have to have a 20 percent effect, a ten
6 percent effect, and it gave a feeling for or gave you
7 the opportunity to say, "Well, geez, if I saw a ten
8 percent effect and a p of .05, that would be good
9 enough for me," or that you'd want to vary that
10 around.
11 So you can, indeed -- it's too
12 complicated.
13 ACTING CHAIRMAN BORER: Okay. Then since
14 it's too complicated --
15 DR. LIPICKY: Yes.
16 ACTING CHAIRMAN BORER: -- we'll avoid it.
17 Let's go on to --
18 DR. LIPICKY: Let's leave the hazard
19 ratios alone.
20 ACTING CHAIRMAN BORER: Okay. We'll go on
21 to number six, which is the same question, but about
22 the secondary endpoints.
23 DR. LIPICKY: But now you have more
24 information. So are you going to change your mind
25 with respect to how much evidence you need for the

1 primary strength of evidence? Because that's the only
2 guy you can really calculate a p value for.
3 ACTING CHAIRMAN BORER: Okay. Tom, do you
4 have any additional comments about that?
5 DR. FLEMING: Well, this one is one that
6 I think is intrinsically difficult to judge. If you
7 have a level of evidence in your primary endpoint, how
8 much influence do you allow secondary endpoints to
9 play or to have?
10 It matters a lot on the relative
11 importance. Lloyd was giving an example earlier of a
12 secondary endpoint that was mortality and had very
13 strong mortality trends or mortality influence.
14 Certainly mortality is a secondary
15 endpoint; if it showed a very striking result, would
16 appropriately influence your assessment of strength of
17 evidence overall, and it, of course, could go in
18 either direction.
19 A study that looked good on the primary
20 endpoint with every unfavorable secondary measures
21 could readily move you away from a judgment of
22 positivity, and the reverse could happen where you
23 didn't hit the primary and you had reinforcement on a
24 secondary measure that was profoundly established and
25 highly clinically relevant, and that should, in fact,

1 substantially influence your judgment in a positive
2 direction.
3 Here I guess what I would throw out is
4 that certainly whereas I had argued that from a
5 traditional perspective we would call it a positive
6 study if we had a significance level less than .02 and
7 it was .01, but not judged as the same strength of
8 evidence as two such studies because that should have
9 been more on the order of .0005 in this setting, and
10 it wasn't close to that.
11 The question is: should the results be
12 influenced or should your interpretation be influenced
13 by secondary measures?
14 I think we're hearing pretty consistently
15 that all of us would say yes. Where it might be more
16 difficult though is to say how much should it
17 influence, and where I've been probing with my
18 colleagues is to try to get a clear sense from them as
19 to whether these secondary measures on symptomatic
20 effects represent profoundly important changes,
21 moderately important changes, modest changes, or
22 relatively trivial changes because that would
23 influence.
24 I wouldn't move greatly on this pathway.
25 I would still be heavily, most heavily influenced,

1 Ray, by the primary endpoint

2 DR. LIPICKY: Right.

3 DR. FLEMING: But I would be somewhat

4 influenced, and how much would depend on these

5 clinical judgments.

6 DR. LIPICKY: Well, in part, to take it

7 out of p values -- let's say that you're selling a

8 watch, and you're asking $1 million for the watch, and

9 someone comes up and says, "Well, I've got 100,000.

10 Isn't that good enough?"

11 Roughly how the primary endpoints line up

12 here, and you look at them and say, "Well, you're very

13 nice looking and you talk to me nice and you're sweet

14 and so on and so forth, and you have all these other

15 things that I like about you. Yeah, that's enough."

16 And that's what we're trying to get a

17 feeling for. How are you putting this together?

18 ACTING CHAIRMAN BORER: I don't think that

19 analogy is apt here, Ray.

20 DR. LIPICKY: You don't think that's --

21 (Laughter.)

22 ACTING CHAIRMAN BORER: Because -- because

23 I think what the $100,000 person may be offering is a

24 little bit more, and I would infer those -- or in some

25 cases a little bit less -- and I would infer that from

1 the sub-analyses that were done, which we haven't
2 gotten up to here yet.
3 So, you know, I think that once again you
4 have to accept this as package. It's a very
5 complicated package. We've not been asked to review
6 an application like this before, to the best of my
7 knowledge.
8 DR. LIPICKY: I understand.
9 ACTING CHAIRMAN BORER: So we're sort of
10 breaking new ground. I think you have to see it as a
11 package.
12 Can I ask? We haven't heard from --
13 DR. LIPICKY: We want -- we want you to
14 clearly outline how you're thinking.
15 ACTING CHAIRMAN BORER: And we will.
16 DR. LIPICKY: Okay.
17 ACTING CHAIRMAN BORER: We haven't heard
18 from Mike Artman down there. Mike, did you have any
19 thinking about this?
20 DR. ARTMAN: Just going on with this
21 package issue, I was very impressed, and Steve alluded
22 to the anatomical and function and physiological
23 changes, but there were also, I think, some very
24 important biochemical changes that we really didn't
25 focus on that provide me with a great deal of

1 additional comfort.

2 The fact that norepinephrine and BNP
3 levels went down in the treatment group and went the
4 other way in the placebo group I think is a very
5 positive finding that if I were the sponsor I would
6 have stressed a lot more.

7 So, again, taking all of this together,
8 drawing on Ray's analogy, yeah, it's 100,000 for the
9 watch, but I'll give you another 250,000 for the band,
10 and you give me a case. There's another 300,000, and
11 now we're getting pretty close to the million that you
12 were asking.

13 ACTING CHAIRMAN BORER: Well, at least
14 we'll give it to you in kind.

15 Dr. Anderson, do you have any thinking
16 about Ray's analogy or anything else with regard to
17 this particular issue?

18 DR. ANDERSON: Mr. Chair, I read these
19 documents, and I had a great deal of difficulty trying
20 to sort things out, and particularly in terms of
21 magnitude, you know, how big should it be and all of
22 that.

23 In reading the FDA reviews, I notice that
24 there were several statements which said we could not
25 draw a conclusion or something to that effect, and I

1 had hoped that in hearing my distinguished colleagues
2 during the discussion I would be able to sort these
3 out and decide which direction to move in.
4 But it seems to me that we're all somewhat
5 perplexed by whatever it is that I can't figure out.
6 So right now I don't really have anything to add to
7 the discussion.
8 ACTING CHAIRMAN BORER: Okay. JoAnn, do
9 you want to weigh in on this before Steve does?
10 DR. LINDENFELD: You know, I don't
11 think -- first of all, I'm not buying any watches from
12 Ray.
13 (Laughter.)
14 DR. LINDENFELD: I think that the
15 strength, as Michael said, too, I think that all of
16 the things are going in the right directions. The
17 neural hormones provides several different areas,
18 neural hormonal findings, echo findings. Those just
19 give me additional; they add to the strength of that.
20 Each one I think separately does when you have those
21 three separate areas.
22 So I think it adds at least a modest
23 amount to the value of the primary endpoint.
24 ACTING CHAIRMAN BORER: Steve.
25 DR. NISSEN: Ray, I think different

1 secondary endpoints should have different value, and
2 you know, for me endpoints that relate to how patients
3 feel are much more important, much more weighty in my
4 view than, you know, some very contrived line.
5 And so I think somebody, you know, that
6 can, in fact, walk without dyspnea, that that ought to
7 have a lot more weight than some finding of JVD on
8 physical examination.
9 And so for me, while I was very impressed
10 by the fact that this constellation was all going in
11 the right direction, the ones that I think as we
12 consider other applications that ought to have, you
13 know, some weight in our minds are ones that relate to
14 how patients feel because that's part of our goal as
15 physicians: make people feel better.
16 And so that did have a lot of weight.
17 Now, how much I think is very hard for me to tell you
18 out of the context.
19 And I'm going to say something equally
20 heretical and say that I view an active control trial
21 a little bit differently than a placebo controlled
22 trial in terms of what I'm looking for in the weight
23 of evidence. You know --
24 DR. LIPICKY: Well, this is placebo
25 controlled. We're talking about Val-HeFT here.

1 DR. NISSEN: Yeah.

2 DR. LIPICKY: And we're talking about

3 whether you are willing to accept the primary

4 endpoint --

5 DR. NISSEN: Sure.

6 DR. LIPICKY: -- and make decisions or

7 whether you're going to let the secondary endpoints be

8 the major things that influence your decision. That's

9 what we're talking about.

10 DR. NISSEN: Yeah, I understand, Ray. I

11 guess what I'm also trying to say is I think that the

12 judgment that I might offer for a trial like this, I

13 might not have the same opinion, you know, in another

14 setting.

15 DR. LIPICKY: Of course.

16 DR. NISSEN: I can't take this out of

17 context very easily.

18 DR. LIPICKY: Of course.

19 DR. NISSEN: Yeah.

20 DR. LIPICKY: But I just want you to say

21 whether you're throwing the primary endpoint away,

22 although it was okay. This was a single trial and

23 you're basing your opinion primarily on the second

24 endpoints which you admit you don't quite know how to

25 evaluate except they look impressive.

1 DR. NISSEN: Well, I didn't say that I
2 don't know how to evaluate them. I mean, I think some
3 people said that, but I guess what I would say is that
4 we fell somewhere between, you know, what we'd like to
5 see for two single trials and we'd like to see for a
6 single trial, and so --
7 DR. LIPICKY: Well, how far between?
8 DR. NISSEN: Well, we were closer to -- we
9 were pretty close to what you'd want to see for, you
10 know, a single trial.
11 DR. LIPICKY: No, no, no. No, no, no, no,
12 no.
13 ACTING CHAIRMAN BORER: That wouldn't make
14 it on a single trial.
15 DR. LIPICKY: Don't misunderstand what
16 went on. It was .09. That's nominal p value, but you
17 could double that. So that's .02. So what you want
18 for two trials --
19 DR. NISSEN: Okay.
20 DR. LIPICKY: -- is half of .00125. So
21 it's .0006. So the .09 is one and a half line
22 segments off.
23 DR. NISSEN: Okay.
24 DR. LIPICKY: Okay? So it's not close in
25 any sense of the word to "close."

1 Yeah, .009.

2 DR. NISSEN: Oh, oh, nine, yeah.

3 DR. LIPICKY: It's still orders of

4 magnitude off, not a little bit, a lot.

5 DR. NISSEN: It's off some.

6 DR. LIPICKY: Some? Ten times.

7 DR. NISSEN: You know, we could quibble

8 about what word to apply to it. I guess --

9 DR. LIPICKY: It's $100,000 to a million.

10 That's how far off it is.

11 DR. NISSEN: Well, all I can tell you is

12 I guess that I do think that the secondary endpoints

13 have a considerable weight in my view, and in this

14 case I think they help me a great deal.

15 DR. LIPICKY: Okay.

16 ACTING CHAIRMAN BORER: Okay. Did you

17 have another comment, Ray?

18 DR. LIPICKY: No, but where are you in the

19 questions?

20 ACTING CHAIRMAN BORER: We're about to hit

21 the meat of the issue here, but, Paul, did you want to

22 make another point here first?

23 DR. ARMSTRONG: I just wanted -- I mean,

24 in my view, the overall effects on secondary endpoints

25 are modest, and I'm guided by sort of five questions.

1 One is the severity of the disease and its impact,
2 mortality/morbidity in terms of what we're dealing
3 with, and there's no argument about this disease.
4 The second is what other proven therapy
5 exists for that disease, and there's no argument about
6 that, and there's also no argument that the patients
7 that we are looking at were treated arguably
8 suboptimally, and we can argue why.
9 The third is the commonality of the
10 problem and its public health implications, and
11 there's no argument about that.
12 The fourth is the consistency of the
13 effect across subgroups, and there are some concerns
14 that we've heard here in terms of coming to a
15 judgment.
16 And the final issue is the hazard of the
17 therapy and its implications across subgroups, and
18 we've had some discussion about that.
19 And so coming back to Ray's question, I
20 put my line between ten and 15 percent relative in
21 this disorder, and how close I am to ten as opposed to
22 how close I am to 15 is modulated by trying to work
23 within that --
24 DR. LIPICKY: Is that line segment one,
25 two, three, or four?

1 DR. ARMSTRONG: It's between about .87 and
2 .9.
3 DR. LIPICKY: I see. Okay.
4 ACTING CHAIRMAN BORER: We're about to
5 enter the phase of dealing with those issues that Paul
6 just talked about, and I think maybe we can come back
7 to or maybe even obviate how important or how
8 significant we think these data are, how important and
9 significant once we go through the next couple of
10 questions.
11 Because here's where the confounders
12 really hit us. Consider the effects on mortality and
13 morbidity endpoints by non-randomized use of ACE
14 inhibitors and beta blockers, and here we have a
15 table. We've seen these data.
16 Which of the following hypotheses are
17 these -- with which of these are the following
18 hypotheses are these data most consistent?
19 Number one, valsartan is an effective
20 treatment added to ACE inhibitor and beta blocker.
21 Can we say that? Can we not?
22 Valsartan is an effective treatment as an
23 alternative to ACE inhibitor or beta blocker. Can we
24 say that?
25 Tom, why don't you lead off and then this

1 is something I think we need some discussion around
2 the table with.
3 DR. FLEMING: All right. Could I ask the
4 sponsor to put up two slides that I'd like to run back
5 and forth very frequently? They're the ES-5 and ES-4
6 slides that I thought provided kind of a good overview
7 of these issues.
8 And actually I might fold in a little bit
9 of the Question 8 at the same time as addressing this.
10 The first part of seven relates to trying
11 to interpret whether valsartan is an effective
12 treatment when added to an ACE inhibitor and a beta
13 blocker, and the second bullet point on eight says --
14 refers to the very small apparent effect in patients
15 taking ACE inhibitors.
16 This is looking at morbidity. I'm going
17 to jump back to ES-4 in a moment, but if we look in
18 those taking ACE inhibitors, which is 92 percent, I
19 think, of the study, we have approximately an eight to
20 ten percent reduction in morbidity.
21 Go to E-4, please.
22 And approximately a seven percent increase
23 in mortality. I look at that in a very subjective way
24 as in Question 8 where it said the very small apparent
25 effect. I look at it as actually data suggesting

1 little to any effect, slight decrease in morbidity,
2 slight increase in mortality.
3 Go back then to E-5, and now we're asking
4 the question about addition to beta blocker, addition
5 to beta blockers. Here's the cohort here of 1,750
6 people where there is for morbidity actually an
7 estimated increase in morbidity not significant.
8 Go to mortality, and it is significant
9 here in mortality, although I use the word
10 "significant" with great caution in subgroups like
11 this, but at least I wouldn't use the words at the end
12 of Question 8 "the apparent treatment effect in
13 patients." I would actually suggest if anything there
14 is a slight suggestion of an adverse effect.
15 Let me go back though to E-5 because I'd
16 like to really step back and look at these results
17 more globally. It is relevant. Certainly I think the
18 sponsor has made a very good case that it's relevant
19 for us to give careful consideration about what is the
20 evidence about effects in the presence or absence of
21 ACE inhibitors and the presence and absence of beta
22 blockers.
23 But it's really important to look at these
24 numbers and realize that we already have to be very
25 cautious about interpreting subgroups. I think there

1 is -- we have three to five percent of the patients in
2 the no/no category and in the no/yes category. In
3 other words, what we're saying is 92 percent of these
4 people are on ACE inhibitors. This study tells us in
5 my view when we start subdividing into subgroups and
6 then focusing on subgroups with three to five percent
7 of the study, to my way of thinking that is really
8 stretching past what these data are able to tell us.
9 So when I look at these data, I would
10 focus as we have here first on the global results, but
11 if we're going to then start looking at subgroups, it
12 seems as though the subgroups that we can say
13 something about are those on ACE inhibitors. It's 92
14 percent, and then subdividing that 92 percent into
15 those that are on ACE inhibitors without beta blockers
16 and ACE inhibitors -- excuse me -- those that are not
17 on beta blockers or on beta blockers, and these two
18 are essentially the same results. These are
19 incredibly unreliable.
20 Essentially as I look at it what we have
21 is the results indicate for morbidity that we have a
22 slightly positive result, although use of beta
23 blockers is a qualitative interaction where we would
24 say, yes, there is a modest benefit when you're on ACE
25 inhibitors adding valsartan, but if you're not also on

1 a beta blocker, it's a bit more of a benefit, but it's
2 a harmful effect if you are on beta blockers.
3 Now go to mortality, and the same basic
4 issue. Here you have a slightly adverse trend when
5 you're on ACE inhibitors, and again you have this
6 qualitative interaction where there's a slightly
7 favorable -- I think it's about a four or five percent
8 decrease and a 40 percent increase, and then, of
9 course, you see the exact same pattern here when you
10 look at those that are exclusively on -- basically
11 those all of whom are on ACE inhibitors.
12 These comparisons are 92 percent ACE
13 inhibitors. These are 100 percent ACE inhibitors, but
14 basically this is the story here. It's what is the
15 effect for people on ACE inhibitors, and when you
16 subdivide those on ACE inhibitors into non-beta
17 blockers and beta blockers, you see a qualitative
18 interaction.
19 My interpretation of these data are if
20 you're on ACE inhibitors, which is 92 percent of the
21 population that are on ACE inhibitors, you have a
22 modest positive effect on morbidity, a modest adverse
23 effect on mortality that seems to be a wash.
24 The data seem to suggest there's an effect
25 modifier here. If you're on ACE inhibitors and you're

1 not on a beta blocker, then it's a slightly or it's a
2 modestly positive effect, but if you're on ACE
3 inhibitors and on beta blockers, it's an adverse
4 effect.
5 If we want to interpret this modestly
6 positive effect, then we have to accept the negative
7 effect here. I'd like to understand. Do we have a
8 theory? Do we have a theory for why it's actually
9 harmful to add valsartan when you're on ACE inhibitors
10 with a beta blocker, but it might be beneficial when
11 you add valsartan when you're on ACE inhibitors, but
12 not a beta blocker?
13 It may be true, but in my experience in
14 interpreting subgroup analyses, there has always been
15 an historical caution used in interpreting subgroups
16 and even greater caution with it's a qualitative
17 interaction rather than a simple quantitative
18 interaction, quantitative interaction meaning, yes,
19 there's effect modification, but it's just a matter of
20 how much benefit by subgroup.
21 Qualitative means harmful in one group,
22 helpful in the other.
23 So in summary, there is certainly very
24 interesting and important evidence here. I find it
25 though very difficult to interpret why it is that

1 valsartan could be beneficial when you're on ACE
2 inhibitors without beta blockers, but harmful when
3 you're on ACE inhibitors with beta blockers.
4 ACTING CHAIRMAN BORER: Okay. Why don't
5 we go down the table and get additional comments about
6 this issue? I think this really is going to be the
7 crux of our final conclusion.
8 Alan, what would you say about -- take
9 seven and eight together just as Tom did if you want
10 to.
11 DR. HIRSCH: Well, I think Tom said it
12 very well. I also pulled out the same two slides, and
13 I think I'll just take off where he left.
14 Didn't we fail today to really examine
15 this potential paradox? Because that is most
16 worrisome to me. I'm concerned with how the
17 implications of these data would be applied in real
18 life practice where we ten to maximize treatment, add
19 drug onto drug.
20 As Ray said earlier, this will be the
21 seventh or eighth drug people are taking. So I don't
22 know. I think to summarize, yes, in addition to an
23 ACE inhibitor alone there is both a potential slight
24 benefit, but potential wash. With both an ACE
25 inhibitor and beta blocker together we have potential

1 net detriment.

2 ACTING CHAIRMAN BORER: Let me just ask

3 you to comment just a little bit further.

4 DR. HIRSCH: Okay.

5 ACTING CHAIRMAN BORER: Question 7,

6 actually the second is not is it any good when you add

7 it onto ACE inhibitor. The question is: is it an

8 effective treatment as an alternative to ACE inhibitor

9 or beta blocker, a slightly different issue for which

10 we've have to make inferences based on those small

11 groups as well as the larger subgroups that Tom

12 pointed out?

13 And in answering this, you know, I want to

14 mention again that there were eight different ACE

15 inhibitors used, and the doses varied across the

16 board, and the targets that Jay talked about that were

17 sort of -- the on average were approached are targets

18 of consensus, not of scientific database because we

19 really don't know the dose response of ACE inhibitors

20 for the hard endpoints for heart failure.

21 There are some data that suggest the more

22 you give the better off you are, but we really don't

23 have any dose response data. So we don't even know

24 what doses people are supposed to be on. They

25 certainly were on a whole load of varying doses.

1 The reason I'm emphasizing this, again, is
2 that if you want to say that we can say something from
3 these data about the additivity of ARBs or of this ARB
4 to an ACE inhibitor, I'd like to know how we can make
5 that statement. My opinion is that we can't say very
6 much.
7 The issue, however, of alternatives to ACE
8 inhibitors is something we need some comment about
9 because that's not the way the trial was done, but we
10 have some data. So --
11 DR. HIRSCH: Why don't we start the
12 discussion and go around the table?
13 DR. FLEMING: Okay. I should have -- what
14 you're pointing out, Jeff, is really there's another
15 step I should have taken in my comments. Basically in
16 my comments what I was referring to were the data that
17 I believe at least answers the first part. Is an
18 effective treatment when added to ACE inhibitor?
19 In my view it's very modestly effective in
20 morbidity, but you have a comparable opposite effect
21 on mortality. So I would say it's very minimal, and
22 when added to a beta blocker, well, certainly it's
23 unfavorable is the estimate.
24 ACTING CHAIRMAN BORER: With ACE inhibitor
25 and beta blocker, yeah.

1 DR. FLEMING: Well, unfortunately, the
2 only data I believe we really have to answer the added
3 to beta blocker with any reliability is in the context
4 of ACE inhibitors because there are very few people
5 without ACE inhibitors and without beta blockers.
6 Is it effective as an alternative to ACE
7 inhibitor? Well, it's a great study. We've got 5,000
8 people. Now we're trying to answer a question based
9 on 366 if you're trying to answer that question. I
10 believe you need a -- if you want an answer to that
11 question, you need another study.
12 DR. HIRSCH: I would agree with that. The
13 sample size is too small despite the point estimated
14 and p value to be really confident.
15 DR. FLEMING: And then is it an effective
16 treatment as an alternative to a beta blocker? There
17 we have some data. We have the ACE inhibitor, yes,
18 beta blocker, no, cohort, but here is where I want to
19 probe because if we accept the favorable pattern
20 there, ACE inhibitor, no beta blocker, then we should
21 be equally accepting the reliability of the very
22 negative result in the ACE inhibitor with beta
23 blocker, and I and to know. My belief is if you're
24 going to put stock in subgroups, there needs to be
25 more than statistical evidence. There needs to be a

1 strong biological plausibility that backs up the
2 argument for why if you're on an ACE inhibitor and
3 you're going to add valsartan when you're not on a
4 beta blocker, that's a good thing to do.
5 But if you're going to add valsartan when
6 you're on a beta blocker and an ACE inhibitor, that's
7 a bad thing. I don't understand the biological
8 rationale for that qualitative interaction.
9 ACTING CHAIRMAN BORER: Okay. Why don't
10 we come back to try to answer that? I mean that gets
11 us into the realm of speculation, and there are a
12 whole load of mechanisms that one might propose to
13 account for a negative interaction when you have
14 multiple neurohumoral systems blocked at the same time
15 and then you add a drug that might cause hypotension.
16 But rather than get into that, let's just
17 move on for a moment to the specific questions here.
18 Tom gave a very comprehensive answer to
19 what we have. Alan, you were about to discuss this
20 again.
21 DR. HIRSCH: If I simply say it at face
22 value to make it simple, let's take both subgroups and
23 take the data as they are without speculating and
24 assume that there is a potential value in the one and
25 a potential adverse effect in the other.

1 ACTING CHAIRMAN BORER: Okay.

2 DR. HIRSCH: Let's go down and see if we

3 see that clinical data the same along the group, and

4 then I think we should bore into mechanisms a little

5 bit.

6 ACTING CHAIRMAN BORER: Okay. Paul.

7 DR. ARMSTRONG: What's the question? Am

8 I answering the first question here?

9 ACTING CHAIRMAN BORER: Number seven.

10 DR. ARMSTRONG: Right.

11 ACTING CHAIRMAN BORER: Valsartan is an

12 effective treatment added to ACE inhibitor and beta

13 blocker. Valsartan --

14 DR. ARMSTRONG: I don't know about the

15 alternative, and maybe it looks like a wash to me

16 relative to the first, and I would be interested in

17 knowing if we're into subgroups whether the

18 characteristics of these subgroups are similar or

19 different.

20 ACTING CHAIRMAN BORER: Okay.

21 DR. LINDENFELD: I can't add to that,

22 except I agree with Paul. We haven't seen a lot of

23 that data to evaluate these subgroups, but I would be

24 hesitant to do it.

25 The only data -- we have previous data

1 that suggest that an angiotensin receptor blocker
2 would be valuable in the absence of other drugs, and
3 that strengthens a little bit this subgroup, but the
4 subgroup not on any other therapy is so small that it
5 makes me very hesitant to interpret it.
6 ACTING CHAIRMAN BORER: Can I just point
7 out, I mean, just so that we keep it in mind because
8 Paul has made a very important point here, and we're
9 going to get to it again in Question 8?
10 The composition of the subgroups is
11 something that is very important to know. However,
12 the trial is a trial. These are the people we got.
13 This is it. So we're going to have to extrapolate as
14 best we can from, you know, an overwhelming group of
15 Caucasians with a very small group of blacks, and on
16 and on.
17 We can try and get down to smaller and
18 smaller subgroups, but then we're getting into
19 potential hot water here. I think we're going to have
20 to take the population here as it was given to us and
21 extrapolate as best we can.
22 Steve.
23 DR. NISSEN: I think we're trying to tease
24 too much out of the subgroups here, and I'm really
25 concerned that we can easily make a mistake by doing

1 so, and you know, it's hard to interpret data, you
2 know, with a few hundred patients in a subgroup either
3 way, either affirmatively or negatively.
4 And so my view is that we have to take the
5 trial as its entirety and say that in a group of
6 patients and maybe even describe this; and in a group
7 of patients, 93 percent of whom or 92 percent of whom
8 were receiving ACE inhibitors, valsartan produced the
9 following benefits.
10 And I am unwilling to make any strong
11 commitment based upon subgroups in a single trial, and
12 I think that this is hypothesis generating for those
13 subgroups, but it is not proof, and therefore, we
14 ought to be very careful here and fairly narrow in our
15 interpretation.
16 ACTING CHAIRMAN BORER: Mike, what about
17 the safety issue here? I mean, you know, a negative
18 result we generally don't require the same degree of
19 statistical certainty when we see detriment, and we've
20 seen detriment here. Mike, can you talk about that a
21 little bit?
22 (Pause.)
23 ACTING CHAIRMAN BORER: Or talk about
24 whatever you'd like to talk about.
25 (Laughter.)

1 DR. ARTMAN: No, let's get back to Ray's
2 watch.
3 No. Yeah, I am concerned about the
4 addition of valsartan to a patient who's on a beta
5 blocker, right. And I agree with everything that's
6 been said coming down the table, and I'm not sure I
7 can shine any more light on this, and to try and make
8 some judgments on these subgroup analyses I agree is
9 very difficult, and we're in treacherous waters.
10 But I think that the data are sufficient
11 to make me very concerned about using this in a
12 patient who is on a beta blocker, and so I think that
13 that part of the question I feel we can't answer.
14 ACTING CHAIRMAN BORER: JoAnn?
15 DR. LINDENFELD: I just think, again, this
16 is a difficult subject, but whether or not we like the
17 subgroups or want to evaluate them, if we choose to
18 recommend this drug for the treatment of heart
19 failure, we're recommending a group of people of whom
20 probably 25 percent it was estimated, maybe a little
21 less than that, but at least 25 percent are taking
22 beta blockers.
23 And I think we're going to have to give
24 people, practicing physicians, some idea of what we
25 think after reviewing this data. I don't think we can

1 just let that drop and say we can't evaluate it. That
2 has to be part of this process.
3 ACTING CHAIRMAN BORER: What would your
4 opinion be?
5 DR. LINDENFELD: Well, I'm very hesitant
6 when I don't know. I'm concerned. There's a very
7 modest benefit to this drug, and there's some
8 potential for harm in at least a quarter of the
9 patients that we're recommending it for, and that
10 makes me feel less positive about the very small
11 benefit that we've seen.
12 ACTING CHAIRMAN BORER: Steve?
13 DR. NISSEN: There is an alternative.
14 There's a way around this, and the way around this is
15 in the context of giving an indication for the drug
16 doesn't preclude adding to the label a warning that in
17 a single trial the combination of the three drugs
18 together in a small number of patients showed an
19 adverse outcome, and so you've told the prescribing
20 physician that the drug has an effect in a broad
21 population, but there was a subgroup.
22 And that protects, I think, the patient,
23 the physician, the agency. It protects everybody
24 until further data can be collected to confirm or
25 refute this notion that triple drug therapy is bad,

1 and that would be to me a logical approach.

2 ACTING CHAIRMAN BORER: Alan?

3 DR. HIRSCH: Can I take this? Because I

4 was going to take you to task, my distinguished friend

5 on the left, Dr. Nissen, because your usual carrying

6 forth that we should not look at subgroups I usually

7 respect, but I've been so quiet all day, troubled by

8 the subgroup data.

9 And this is not a small subgroup. I mean,

10 1,600 --

11 DR. FLEMING: Right.

12 DR. HIRSCH: -- more or less patients --

13 DR. FLEMING: Steve, I wanted to follow up

14 on that, too.

15 DR. HIRSCH: -- is significant.

16 DR. FLEMING: Yeah, it's 1,750 in what

17 you've called a small subgroup. Can we flash up --

18 DR. HIRSCH: I'm not quite done.

19 DR. FLEMING: Go ahead. Go ahead.

20 DR. HIRSCH: The subgroup actually

21 following Dr. Cohn's line of reasoning is actually

22 hopefully going to be growing as we become more

23 aggressive in the treatment of heart failure, and we

24 don't quite know yet what's down the pike in terms of

25 the ability to both educate physicians. Other trial

1 data will have us adding more and more agents.

2 So when I look at this historically,

3 actually the first signal where we finally hit sort of

4 a wall potentially, we should as an agency or as an

5 advisory panel be concerned.

6 So just that point has been made. I feel

7 very strongly we have to respect that subgroup at

8 least as a -- more than a hypothesis generation, but

9 as a time right now to educate physicians to be

10 careful.

11 ACTING CHAIRMAN BORER: Tom, did you have

12 an additional point you wanted to make?

13 DR. FLEMING: That was well spoken. I was

14 just going to, if we could put up for a moment again

15 E-4 and E-5.

16 Just to reiterate, here is where the data

17 are. The data are in these three groups, and, Steve,

18 this is a -- I mean, your comments are wise, causing

19 us -- encouraging us to be cautious about subgroups.

20 I consider that a very wise comment.

21 At the same time, there is something here

22 that's not easy to walk away from, and I would concur

23 with the sponsor raising this issue as one that has to

24 be seriously considered. I look at the analysis in

25 these three groups as where the essence of the