

1 DR. COHN: Yeah, it comes out the same.

2 DR. FLEMING: The main answers are if you
3 look at those on ACE inhibitors, which is 92 percent
4 of the cohort, you see a very small increase in
5 morbidity and a very small worsening of mortality, a
6 net comparable result.

7 ACTING CHAIRMAN BORER: Paul.

8 DR. ARMSTRONG: Jay, although the number
9 of blacks was small, it was comparable to the subgroup
10 analysis in size of the patients not on ACE
11 inhibitors. So I wanted to ask you a series of
12 questions related to that population.

13 First, from the knowledge that you or the
14 company has, what is the information on the anti-
15 hypertensive effect of valsartan in blacks?

16 Second, do we have information on the
17 hormonal and the morbidity data in blacks vis-a-vis
18 whether this trend, if you will, which is not
19 significant on mortality, is supported by some of the
20 other ancillary measures that you so eloquently
21 discussed in the other subgroups?

22 DR. COHN: Malcolm can probably answer the
23 question.

24 MR. MacNAB: I can answer the first one.
25 The package insert for valsartan states that the

1 efficacy in whites and blacks for hypertension is
2 about the same. That's what the database that we have
3 shows.

4 ACTING CHAIRMAN BORER: What about the
5 renin angiotensin profile?

6 DR. COHN: Yeah, let me answer your first
7 question here. Can we get that? Yeah.

8 This is the breakdown, if you wish, for
9 plasma norepinephrine mean change from baseline, and
10 you'll notice that the blacks appear to exhibit the
11 same difference as do the whites in terms of lowering
12 norepinephrine.

13 So from a hormonal standpoint there
14 doesn't appear to be a racial difference in response.

15 DR. HIRSCH: And was there a mortality
16 difference in the subgroup?

17 DR. COHN: In the blacks there was a trend
18 in the other direction, right. None of it was
19 significant; very wide confidence intervals.

20 ACTING CHAIRMAN BORER: Do you have -- I
21 mean these are norepinephrine. Do you have renin data
22 on the --

23 DR. COHN: No, we have norepinephrine and
24 BNP only. That's the only two hormones that we
25 monitored, and the BNP also exhibited, I think, the

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1 same.

2 Well, here. Okay. We can give you this,
3 too. Boy, my team has more slides there.

4 All right. Here's the BNP data just for
5 completeness. Now, with BNP there did appear to be a
6 difference. That is, all these other groups show a
7 favorable effect of valsartan compared to placebo. In
8 the black patients that was not true. So now we find
9 a differential between BNP and norepinephrine.

10 I mean, you can chew on this all you want
11 to. I don't know what to make of these data.

12 And then we also have the mortality data
13 that was addressed. I'll give you that data directly.
14 Can we have that mortality slide and the racial
15 breakdown?

16 Here we are. This is black patients.
17 This is mortality. You can see the trend was in the
18 wrong direction. Obviously wide confidence intervals.
19 This is morbidity, a trend in the wrong direction, and
20 these were in the non-black patients in terms -- and
21 mortality obviously.

22 Now, turning down to .997 and morbidity
23 being strikingly better. So we obviously have no
24 answers. This is retrospective analysis.

25 ACTING CHAIRMAN BORER: Okay. Why don't

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1 we hold any other issues for Jay for his next
2 presentation?

3 And we'll move on now to the safety --

4 DR. NISSEN: Jeffrey we going to --

5 ACTING CHAIRMAN BORER: Oh, I'm sorry.
6 Just one moment.

7 DR. NISSEN: Are we going to come back to
8 the adjudication?

9 ACTING CHAIRMAN BORER: Yeah, right. What
10 I was just remembering is that we have the
11 adjudication issue that we can deal with. Why don't
12 we take care of that now?

13 DR. NISSEN: Before you got here, we all
14 had a number of questions, and I want to see if I can
15 focus on some of them. Since endpoints were not
16 independently adjudicated, we want to understand the
17 process, and I guess I'd like to understand who
18 identified the cases for adjudication, what triggers
19 did they use, what source documentation was provided.
20 You know, was it a narrative? Did you review the
21 charts? Did you get excerpts from the charts?x

22 And then the third question I had was I
23 present a hypothetical case of somebody that came in
24 at nine o'clock in the morning with an exacerbation of
25 heart failure, was admitted, got intravenous

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1 furosemide for the day, and then that evening went
2 home; whether that would have been considered a heart
3 failure hospitalization.

4 DR. CARSON: Let me just say, first, I'm
5 sorry to make you all go back on this. I must say it
6 is probably easier to fly to the NIH than to drive
7 across town to here.

8 You started off with a comment that they
9 were not independently adjudicated.

10 DR. NISSEN: Right.

11 DR. CARSON: I'm not sure I understand.

12 DR. NISSEN: Well, the sponsor presented
13 cases to the committee for adjudication. The
14 adjudication committee was not independent of the
15 sponsor.

16 Independent adjudication means that
17 somebody who's independent of any other interests in
18 the trial, you know, gets source documentation, does
19 adjudication. That's not what happened here.

20 DR. CARSON: Okay. I don't know of any
21 endpoint committee that has been associated with any
22 trial that has been independent in a way that we
23 weren't, and I actually have done more of this than
24 probably anybody else.

25 DR. COHN: Can you speak up, Peter? I

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1 don't think everybody can --

2 DR. CARSON: Well, I'm just saying I don't
3 know of any way that this committee was not
4 independent than any other committee associated with
5 any large trial has not been independent. We were
6 blinded. None of us were investigators in the trial,
7 and the materials were provided to us, it is true, by
8 the company, but this is as independent as any
9 committee I've ever been associated with.

10 In terms of the materials that we
11 received, we required that there be primary source
12 documentation. So we asked for some hospitalization
13 record, particularly a discharge summary. We often
14 received a discharge summary and an initial history
15 and physical exam narrative. We sometimes received
16 hospitalization data.

17 Now, from the U.S., that data was stronger
18 because that data is easier to find, and in some
19 countries, as I understand it, hospitalization records
20 really cannot be obtained, and in those cases then we
21 relied on a letter from the physician taking care of
22 the patient to another physician, referring physician,
23 for example, or a physician involved in enrolling the
24 patient in the trial.

25 So there was always primary documentation

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1 obtained. There was also a narrative from the
2 physician that described the event, whether it was a
3 death or a hospitalization. So there was primary
4 source documentation on virtually every patient unless
5 towards the end of the trial multiple attempts had
6 been made and there simply was no response.

7 In terms of the specific patient that you
8 posed, we realized, I think, after the first meeting
9 we had put in a barrier that said in order to be a
10 heart failure hospitalization you had to have been in
11 the hospital for longer than 24 hours because we
12 assumed that would make it then a serious event.

13 And we found relatively early that it was
14 very difficult to get exact times, and so somebody
15 went back and said, "Well, how did you know it was 24
16 hours?"

17 Getting the exact times turned out to be
18 quite difficult, and this has been true in other
19 trials also.

20 So we then put in the barrier of saying
21 that we may not know the exact times, but if the
22 calendar date changed, we would take that as being a
23 surrogate for a 24-hour admission. So if the calendar
24 date changed, that's what we took.

25 Now, did it happen that there were

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1 patients that were admitted at six o'clock in the
2 morning, got an IV dose of diuretic, and went home at
3 nine o'clock at night?

4 It may have happened. We would not have
5 taken them as being a hospitalization. They not have
6 had a calendar day change. I have to say in my own
7 experience in heart failure that is a very unusual
8 circumstance, and --

9 DR. NISSEN: You would not have even seen
10 those charts then? They wouldn't have come to you?

11 DR. CARSON: I'm not sure whether we would
12 have seen them or not. I think early on we may have
13 seen them, and we may have then said it didn't meet 24
14 hours. So we don't need to see this one.

15 Now, you did --

16 ACTING CHAIRMAN BORER: Those require an
17 assay.

18 DR. CARSON: I would also answer one part
19 of your question, I guess, which was what about the
20 cases that did not come to us. We looked at the work
21 load of the committee, and we adjudicated something on
22 the order of was it 4,100 events? It was just a large
23 number of events.

24 Initially we were seeing all
25 hospitalizations. Initially we were seeing second

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1 hospitalizations after the initial heart failure
2 hospitalization.

3 But then it became apparent that the work
4 load was extreme and that it was just not going to be
5 possible to gather members together, have meetings,
6 and actually adjudicate cases.

7 Now, you can sit and do five an 600 and
8 800 cases in a day, but you're just turning pages, and
9 so in order to actually have discussion of cases and
10 consideration, we felt the work load had to be altered
11 a little bit, and one alteration was that after a
12 patient had a first heart failure hospitalization, we
13 did not adjudicate after that. They had met the
14 primary endpoint.

15 But secondly, patients who had a clear
16 non-cardiovascular cause for hospitalization, we did
17 not see them. The first couple of meetings we did see
18 them, and we became confident as a committee that the
19 sponsor could recognize a non-cardiovascular
20 hospitalization.

21 And then each meeting I would get a list
22 of the non-cardiovascular hospitalizations, and if
23 there was anything that had a primary cause from the
24 investigator that looked like it might have involved
25 heart failure, then we said, "Please send us that,"

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1 and we got it.

2 ACTING CHAIRMAN BORER: Does that -- Paul?

3 DR. ARMSTRONG: I just would like to
4 follow up and also make a comment. For some of us,
5 this adjudication process has involved evaluating data
6 triggered by a data organization that is independent
7 from the sponsor. So I think the spirit of Dr.
8 Nissen's question and my comment apropos of your
9 issue, I'm not questioning the integrity of your
10 committee. Our question was what triggered your
11 opportunity to evaluate things independently, and
12 there are different models, and you obviously used
13 one, but there are others.

14 As I understand it from the briefing
15 booklet, at some point there was an addendum to your
16 committee perhaps driven by the work load in which
17 over diuresis or drug toxicity were perceived as
18 hospitalization for reasons other than heart failure.

19 And I just want to be 100 percent certain
20 then that someone with syncope due to dehydration,
21 digitalis intoxication or hyperkalemia, all things
22 that we as clinicians care for in our heart failure
23 patients, would be a hospitalization that would be
24 perceived not related to heart failure and you would
25 not have seen.

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1 DR. CARSON: No, we would have. We would
2 have seen that. In fact, we were particularly
3 sensitive to that particular area.

4 One of the two areas that we had a
5 particular alarm bell about was the group of patients
6 who could be poor perfusion and poor perfusion with
7 hypotension, poor perfusion with renal insufficiency
8 leading to digitoxicity, et cetera, et cetera.

9 That was a group that we were very
10 concerned about, and so anything that even looked like
11 that, if I saw that on the non-cardiovascular list, if
12 I saw renal failure, if I saw anything cardiovascular
13 we've got, but if I saw renal failure, I said, "I want
14 to see that and make sure it's not poor perfusion."

15 The other group that we were very
16 concerned about was the abdominal pains. Could that
17 be passive congestion leading to abdominal pain? So
18 that was another group that we really targeted. We
19 had to see all of them.

20 DR. ARMSTRONG: Thank you.

21 ACTING CHAIRMAN BORER: Okay. Thank you
22 very much.

23 If there are no other issues about the
24 adjudication process, why don't we try and move on to
25 safety data now? We'll have a little discussion

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1 afterwards.

2 DR. COHN: All right. Bob Glazer will
3 present the safety data.

4 Bob.

5 DR. GLAZER: Safety of valsartan was
6 evaluated in eight clinical trials worldwide that
7 included over 6,000 patients with chronic heart
8 failure. During this presentation I would like to
9 summarize for you the valsartan safety database,
10 including patient exposure, demographics, adverse
11 events, including severe adverse events, and treatment
12 discontinuations, and laboratory evaluations.

13 Valsartan safety database for heart
14 failure consisted of eight clinical trials. There
15 were four placebo controlled trials, one positive
16 control trial, and three open label trials.

17 The primary data set includes the four
18 double blind control trials with trial durations of up
19 to four months and also the first four months of
20 safety data from Val-HeFT. There were over 6,000
21 patients in this primary data set of which 3,289
22 patients received valsartan. The long-term safety
23 data set is comprised solely of data from Val-HeFT.
24 The focus of this presentation will be on these two
25 data sets, namely, the pooled, short-term, primary

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1 data set and the long-term data from Val-HeFT.

2 There were only 94 total patients in the
3 open label trials, and therefore, these data were not
4 pooled for any analysis.

5 The five completed double blind trials
6 consisted of two small hemodynamic studies, Studies
7 103 and 104; two trials whose primary efficacy
8 variable was exercise tolerance, Studies 106 and 110;
9 and the large morbidity and mortality trial, Val-HeFT.

10 All trials except Study 110 evaluated
11 twice daily dosage regimens of valsartan which ranged
12 from 40 milligrams to 160 milligrams twice daily,
13 depending on the particular study. All trials were
14 parallel design and included patients in New York
15 Heart Association Class II, III, and IV, with the
16 exception of Study 110 that excluded Class IV
17 patients.

18 Most trials had an inclusion criteria for
19 ejection fraction requiring patients to have ejection
20 fractions less than either 40 or 45 percent.

21 In the primary data set, which included
22 trials with the maximum trial duration of four months
23 and also the first four months of Val-HeFT, over 3,200
24 patients were exposed to valsartan for at least one
25 day. Over 2,700 patients were exposed to valsartan

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1 for at least three months.

2 Long-term exposure from Val-HeFT included
3 over 2,100 patients for at least six months,
4 approximately 2,000 patients for at least one year,
5 and over 1,000 patients for two years or more. The
6 majority of patients in each time category were
7 exposed to the highest dose of valsartan, namely, 320
8 milligrams total daily dose, as these patients were
9 force titrated to that dose in Val-HeFT.

10 Overall there were no clinically important
11 differences in baseline characteristics between the
12 valsartan and placebo treatment groups in the primary
13 data set. The mean age of the studied population was
14 63 years of age. The number of patients above and
15 below the age of 65 was similar in each treatment
16 group. Approximately 15 percent of patients were over
17 the age of 75 years.

18 Ninety percent of patients were white, and
19 approximately eight percent were black. The majority
20 of patients, 80 percent, were male.

21 The duration of heart failure in these
22 patients was just over four years. The ejection
23 fraction was 27 percent. The mean blood pressure was
24 approximately 124 millimeters of mercury systolic and
25 75 millimeters of mercury diastolic. The majority of

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1 patients, 61 percent, were Class II and 37 percent
2 were Class III.

3 Investigators were asked to select the one
4 primary etiology of patient's heart failure in all but
5 one trial. Coronary heart disease was chosen as the
6 primary etiology in the majority of patients, 57
7 percent, followed by idiopathic cardiomyopathy,
8 hypertension, and other miscellaneous causes.

9 The majority of patients were receiving
10 ACE inhibitors, approximately 90 percent; diuretics,
11 85 percent; and digoxin, approximately 68 percent.
12 Approximately one third of patients were receiving
13 beta blockers and one third were receiving nitrates.

14 Patient disposition was collected
15 differently in Val-HeFT than in the other trials.
16 Therefore, these data were not pooled into the primary
17 data set. The patient disposition data from Val-HeFT
18 has already been presented by Dr. Cohn.

19 In the remaining trials shown here,
20 patient disposition was similar to that observed in
21 Val-HeFT. The most common reason for premature trial
22 termination was an adverse experience occurring in
23 nine percent of valsartan patients and four percent of
24 placebo patients.

25 In the primary data set the incidence of

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1 adverse events regardless of trial drug relationship
2 was 73 percent with valsartan and 69 percent with
3 placebo. Dizziness and hypotension were the two most
4 frequently reported events, and each occurred more
5 frequently in valsartan treated patients than those
6 patients receiving placebo. Dizziness and hypotension
7 were reported in 17 percent and seven percent of
8 valsartan patients, respectively.

9 The incidence of cough in this population
10 was similar in both treatment groups.

11 Similar to this short-term primary data
12 set, the two most frequent adverse events in Val-HeFT
13 shown here were dizziness and hypotension, each
14 occurring more frequently in the valsartan group
15 compared to placebo.

16 The incidence of aggravated heart failure
17 was less in the valsartan group compared to placebo.
18 Diarrhea occurred slightly more frequently with
19 valsartan.

20 In the primary data set, there were no
21 clinically important differences among subgroups,
22 including age, gender and race in the overall
23 incidence of adverse events compared to the overall
24 population. Slightly more female patients compared to
25 male patients reported adverse events in both

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1 treatment groups.

2 Dose response information can best be
3 assessed using the data from Study 106, which was a
4 fixed dose, placebo controlled, parallel design trial
5 that evaluated three different valsartan doses. In
6 this trial, the overall incidence of adverse events in
7 each of the three valsartan treatment groups was less
8 than or approximately equal to that observed with
9 placebo.

10 There was no dose related effect for the
11 more frequently reported adverse experiences,
12 including dizziness and hypotension. A suggestion of
13 a dose response was observed for hyperkalemia, which
14 was reported in one, three, and four percent of
15 patients in the 80, 160, and 320 milligram dose
16 groups, respectively.

17 Summarizing the data from the adverse
18 event case report form in Val-HeFT, permanent
19 treatment discontinuation occurred in 9.9 percent and
20 7.3 percent of patients receiving valsartan and
21 placebo, respectively. A significant difference in
22 rates of discontinuation occurred for dizziness, renal
23 impairment, elevated serum creatinine, diarrhea, and
24 hyperkalemia.

25 The overall discontinuation rates for

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1 adverse experiences in the other control trials were
2 similar to that observed in Val-HeFT.

3 Both sitting and standing blood pressure
4 were measured at all visits in Val-HeFT. At all time
5 points post baseline there was a consistent and
6 significant reduction in both sitting systolic blood
7 pressure, approximately four millimeters of mercury
8 placebo subtracted, and diastolic blood pressure
9 approximately two millimeters of mercury placebo
10 subtracted in the valsartan treated patients.

11 The incidence of serious adverse events in
12 Val-HeFT were similar with valsartan, 51 percent,
13 compared to placebo, 54 percent. The most frequent
14 serious event, aggravated heart failure, and also
15 atrial fibrillation were reported less frequently in
16 patients treated with valsartan. No other significant
17 differences between treatment groups were observed.

18 In the short-term primary data set, the
19 occurrence of serious adverse events was generally
20 similar in each treatment group. Again, aggravated
21 heart failure occurred less frequently in patients
22 receiving valsartan. Incidence rates for individual
23 adverse events were generally less than one percent.

24 The most common cause of death in Val-HeFT
25 as reported by the investigators is shown here, was

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1 sudden death, which occurred in nine percent of
2 patients in each treatment group.

3 Pump failure was the next most frequently
4 reported cause of death. In the remaining four
5 control trials, the number of deaths was small, 14 in
6 total.

7 Noteworthy laboratory changes observed in
8 the valsartan heart failure program relate
9 specifically to the pharmacology of inhibitors of the
10 renin angiotensin system, and include changes in renal
11 function.

12 Small increases in serum creatinine,
13 potassium, BUN, and uric acid were observed in those
14 patients receiving valsartan compared to placebo as
15 shown here.

16 Specific criteria were prespecified to
17 define clinically meaningful changes from baseline in
18 laboratory parameters. For creatinine, BUN, and uric
19 acid a 50 percent increase was defined; for potassium,
20 a 20 percent increase or decrease was defined.

21 In the short-term primary data set, four
22 percent of valsartan patients versus one percent of
23 placebo patients had an increase in serum creatinine.
24 Ten percent versus five percent had an increase in
25 serum potassium, and 17 percent versus six percent had

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1 an increase in BUN.

2 In summary, valsartan in doses of 80
3 milligrams to 300 milligrams once per day was well
4 tolerated in patients with New York Heart Association
5 Class II, III, and IV heart failure. The adverse
6 events observed were not unexpected and included
7 dizziness, hypotension, and postural dizziness.
8 Dizziness and hypotension were the most common reasons
9 for discontinuation of therapy.

10 Laboratory changes included increases in
11 creatinine, BUN, potassium, and uric acid.

12 Valsartan's safety profile in heart
13 failure patients was consistent with the pharmacology
14 of an agent affecting the renin angiotensin system and
15 also the background therapies these patients were
16 receiving.

17 ACTING CHAIRMAN BORER: Thank you very
18 much.

19 Are there specific safety questions from
20 the committee? JoAnn.

21 DR. LINDENFELD: I know there were a small
22 number of patients on spironolactone at the start of
23 the study, but can you give us some idea in that small
24 number of patients what the incidence of adverse
25 events was? Patients on both ACE inhibitors and

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1 spironolactone, and then between placebo and
2 valsartan.

3 And I think this is an important point
4 because aldactone is used substantially more now than
5 I think it was in the baseline group of patients here.
6 So it's something we have to consider.

7 DR. GLAZER: We have just started looking
8 at this topic. We have some laboratory data which
9 showed that there was an increase in the number of
10 patients who made the pre-specified criteria for
11 creatinine.

12 DR. LINDENFELD: I guess creatinine and
13 potassium would be the two we'd be most interested in.

14 DR. GLAZER: Can I have Slide 020?

15 There was a small number of patients
16 receiving background spironolactone, and as you can
17 see in this slide, the percentage of patients who had
18 an increase in potassium was essentially similar to
19 that that was seen in the overall population. The
20 patients who had an increase in serum creatinine are
21 greater than 50 percent above baseline, was greater in
22 those patients receiving spironolactone.

23 Similar incidence rates were seen for BUN
24 and uric acid, again, compared to the overall
25 population.

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1 This patient population has to be -- we're
2 further investigating the laboratory data and safety
3 data.

4 DR. LINDENFELD: I guess it's important.
5 We don't know how many of these were on ACE inhibitors
6 and were not?

7 DR. GLAZER: I don't have that
8 information.

9 DR. LINDENFELD: Because we might expect
10 that those on both would have even a greater
11 incidence. The incidence of withdrawal, I think, on
12 Slide No. 7 shows withdrawal was much greater in
13 patients on spironolactone.

14 DR. GLAZER: Correct.

15 DR. LINDENFELD: And it just becomes an
16 issue because we're using spironolactone a lot more
17 than the small number of patients that were in this
18 trial.

19 ACTING CHAIRMAN BORER: What kind of
20 monitoring recommendations is the company making with
21 regard to electrolytes, BUN, creatinine? Any in your
22 proposed labeling?

23 DR. GLAZER: Yes. As with the care of any
24 patient with congestive heart failure, careful
25 attention should be paid to monitoring BUN, creatinine

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1 and potassium in these patients who were concurrently
2 receiving diuretics, beta blockers, as would be
3 expected.

4 ACTING CHAIRMAN BORER: JoAnn?

5 DR. LINDENFELD: One other question. Can
6 you tell us what the incidence of the requirement for
7 dialysis was in the two arms?

8 DR. GLAZER: The number of patients who
9 had dialysis actually was similar in -- this slide
10 shows the number of patients requiring dialysis in the
11 overall congestive heart failure patients, and you can
12 see that there was 12 patients total receiving
13 valsartan and 12 patients receiving placebo. All but
14 one of those patients were in Val-HeFT. One patient
15 was in Protocol 106.

16 ACTING CHAIRMAN BORER: Paul.

17 DR. ARMSTRONG: As I understand it, 15
18 percent of the patients were over the age of 75, and
19 I wonder if you could develop for me any information
20 you have regarding the relationship between some of
21 the serious adverse events and obviously the
22 hyperkalemia and the creatinine and any others that
23 are of interest in that important very elderly
24 population.

25 Do you have data on that point?

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1 DR. GLAZER: We don't have any laboratory
2 data or adverse experience data cut by the 75 year of
3 age point.

4 DR. ARMSTRONG: And the second question
5 coming back to the issue of efficacy in blacks was,
6 again, the serious adverse events in the creatinine
7 and the potassium issues in the blacks since we don't
8 have the renin angiotensin system measured, but
9 indirectly we might be able to get at it.

10 Do you have any information on that
11 subgroup vis-a-vis serious adverse events and some of
12 the metabolic factors?

13 DR. GLAZER: Can I have Slide 023?
14 Actually it's AEO-17.

15 This information is adverse events by
16 racial subgroups looking at the most frequent adverse
17 events overall, and then looking at the subcategories
18 by race.

19 And essentially, with the exception of
20 chest pain, congestive heart failure and cough, which
21 seem to be reported more frequently in African
22 Americans and black patients in this population, there
23 didn't seem to be any marked differences, though the
24 number of black patients is small and the percentages
25 have to be interpreted cautiously.

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1 DR. ARMSTRONG: Thank you.

2 ACTING CHAIRMAN BORER: Any other
3 questions? Ray.

4 DR. LIPICKY: It doesn't appear as though
5 there are dose limiting side effects, that is, there
6 aren't any side effects that come out as a function of
7 dose. Is that a correct interpretation?

8 DR. GLAZER: From Protocol 106, with the
9 exception of hyperkalemia and possibly if you pull out
10 the MEDRA (phonetic) term postural dizziness, there
11 didn't appear to be any dose related effects in that
12 parallel designed trial, which included about a --

13 DR. LIPICKY: From any other trial that
14 you have that shows dose limiting side effects?

15 DR. GLAZER: I believe in the hemodynamic
16 trial, with the exception of the laboratory events as
17 you would expect with potassium, there were no adverse
18 events in that small, parallel design, hemodynamic
19 trial that showed any --

20 DR. LIPICKY: Can you then tell me what
21 the process, the thinking process, was for deciding
22 that the top dose you studied was the best dose to
23 study?

24 DR. GLAZER: The dose was chosen based on
25 the hemodynamic trials, and we wanted to --

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1 DR. LIPICKY: Yes. So just where does it
2 fit on the dose response curve do you think? The low
3 end, the high end or where since you don't have any
4 reason to -- from adverse effects to not have
5 increased the dose?

6 MR. MacNAB: Dose selection was based on
7 several factors. One, from the hemodynamic trials
8 that you saw where one clearly had much better dose
9 response than the other, but in the both clearly the
10 160 b.i.d. gave the most effect.

11 DR. LIPICKY: But --

12 MR. MacNAB: There was --

13 DR. LIPICKY: -- it was also consistent
14 with the dose response still going up.

15 MR. MacNAB: That's correct.

16 DR. LIPICKY: Right. So it didn't tell
17 you you got to the top.

18 MR. MacNAB: I mean you get to a point of
19 some practicability in that, too. I mean, the 160 --

20 DR. LIPICKY: No, no, no.

21 MR. MacNAB: -- tablets are pretty big,
22 but I just want to finish.

23 All right. We did see a sense of the dose
24 response in a little bit of potassium in 106. If you
25 go back to some very, very early studies done of the

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1 angiotensin infusion studies in normal volunteers
2 where the pharmacodynamics of hypertension appeared to
3 be at 24 hours, you really need to go up to higher
4 doses to get full suppression of the system, and it
5 was generally believed, theoretically at least, to see
6 optimal effects that you needed the most suppression
7 of the system that you could get.

8 So I think based upon those angiotensin-1
9 infusion studies, while in normal volunteers and not
10 perfect, it was one the hemodynamics; a little bit of
11 potassium that we saw; the 160; and just the practical
12 fact that, you know, a 160 milligram capsule of
13 valsartan is not --

14 DR. LIPICKY: Big.

15 MR. MacNAB: -- is pretty big as it is;
16 that putting that all together, that seemed the best
17 to do. Now, obviously it would have been great if we
18 had done a, you know, 50, 60,000 patient trial with
19 multiple arms and multiple doses, but again, that's a
20 practical matter.

21 So it was a sum total of all those reasons
22 is why we picked that dose, and it could have been too
23 high, could have been too low. That's the best we
24 could do with what we had.

25 ACTING CHAIRMAN BORER: Alan.

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1 DR. HIRSCH: Well, to come back to the
2 same questions, I'm not sure I -- I'm not sure I'm on.

3 (Laughter.)

4 DR. HIRSCH: I could raise my voice.

5 Could we come back to safety Slide 14?

6 I'm not sure, as Ray said, that I'm seeing
7 a dose dependent adverse effect profile that worries
8 me, but nevertheless, let me just explore the data if
9 that's why we're here.

10 I just want to see if you can help me
11 understand the sort of negative dose response for
12 dizziness and for hypotension. Does this mean that
13 the physicians stopped the dose titration at 80
14 because they perceived or someone perceived dizziness
15 and hypotension as being an end effect?

16 DR. GLAZER: This was a parallel design
17 trial. They were on a fixed dose.

18 MR. MacNAB: One, oh, six was parallel.
19 There was no -- it was a fixed dose.

20 DR. HIRSCH: One, oh, six. Sorry.

21 DR. GLAZER: That's why we couldn't use
22 Val-HeFT, because of the forced titration. This is
23 the only trial you can get pure dose response
24 information.

25 MR. MacNAB: I mean, overall, if you

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1 looked at all of valsartan data and from
2 hypertension, heart failure, there is not a real dose
3 response for side effects.

4 DR. HIRSCH: Right. I didn't see it
5 either.

6 MR. MacNAB: I mean you have to really
7 dig. Now, I imagine we could give a 1,000 milligram
8 capsule, but for what we've seen up through 160 or
9 through these trials, no.

10 ACTING CHAIRMAN BORER: Okay. If there
11 are no other questions about safety at this point,
12 although we can always revisit that a little bit
13 later, we'll take our break now and come back and have
14 the risk-benefit or the benefit-risk discussion after
15 the lunch break and then go through any additional
16 discussion and the questions we've been presented.

17 We'll take 45 minutes. So we should be
18 back here ready to start at 12:30.

19 (Whereupon, at 11:40 a.m., the meeting was
20 recessed for lunch, to reconvene at 12:30 p.m., the
21 same day.)

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