

1 erratic from the other trials and really where Diana
2 is probably kicking in here to an extent.

3 These six and two long term deaths, are
4 they coming from Diana?

5 DR. OGRINC: Yes.

6 DR. FLEMMING: Yes, and so that is
7 reassuring, but my concern about it is it's sporadic
8 because it's only coming from that one small study,
9 and it does make me think that there is less reason to
10 be concerned about the 15 versus five when I look at
11 the Diana results, but not fully reassured because
12 we're now looking at a more uniform capture of longer
13 term follow-up.

14 DR. ARMSTRONG: And you're also not
15 looking at as large a sample size.

16 DR. FLEMMING: That's true, too.

17 DR. WOLFSON: Could you go to the causes
18 of death please?

19 Okay. This slide does show the causes of
20 death in all controlled clinical trials, and as you
21 can see, cardiac events were the most common cause of
22 death in both groups. This is not unusual given that

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1 cardiac events are the most common cause of death and
2 reflect about 50 percent of the causes of death in the
3 U.S. end stage renal disease population.

4 The other causes of death are the smaller
5 numbers, and there are no differences between the two
6 groups.

7 DR. ARMSTRONG: So another way of looking
8 at this, just to play devil's advocate, which is why
9 we're here, to play the role of the devil, is if I
10 take all of these causes of death and I take sort of
11 the cardiovascular, thromboembolic, vascular causes
12 and pool them, which would be cardiac arrests or MIs,
13 stroke, peripheral vascular disease, bowel infarction,
14 you could potentially see a signal at a time when
15 there is both deaths that are in excess in a high risk
16 population.

17 I don't know. I'm not a nephrologist, in
18 this plasma load of Icodextrin, slide 21, just makes
19 you question it. That's why we're here.

20 DR. FLEMMING: I wonder, just to go on on
21 the point, were the stroked adjudicated?

22 You point out that hypertension is an

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1 important side effect of this compound, and I wonder
2 if I could get some further clarification on the CVA.
3 Were these several hemorrhages? Were they oleic
4 strokes? Were they adjudicated? Do we have CT scans?

5 DR. WOLFSON: No. And I should say that
6 hypertension as an adverse event which was reported
7 during the clinical trials was just reported from the
8 line listings as hypertension or hypertension
9 increasing.

10 Hypertension is also very common in the
11 end stage renal disease population, and in fact, was
12 more common in the baseline period, you know, at
13 baseline in the patients treated with Extraneal, but
14 we have really no information, not a lot of
15 information on the various aspects of any of the
16 deaths. We do have narratives that describe them, but
17 they don't provide a lot of information regarding the
18 type of stroke, for example, or exactly what caused
19 the death.

20 CHAIRMAN BORER: JoAnn?

21 DR. LINDENFELD: Can you tell me when you
22 have this large load of Icodextrin what happens to

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1 plasma viscosity?

2 DR. WOLFSON: Plasma osmolarity --

3 DR. LINDENFELD: No, viscosity.

4 DR. WOLFSON: -- increases slightly.

5 DR. LINDENFELD: Not osmolarity but
6 viscosity.

7 DR. WOLFSON: We have not studied plasma
8 viscosity in these patients.

9 DR. LINDENFELD: It's a large molecule.
10 Would we expect that it would change?

11 DR. BORER: Well, it's not -- presumably
12 it doesn't get into the plasma in large quantities,
13 does it?

14 DR. LINDENFELD: Well, I think that slide
15 they showed us suggested that it does.

16 DR. ARMSTRONG: Well, no, of course it
17 does.

18 DR. LINDENFELD: I mean that's a fairly
19 large quantity. What I'm concerned about is just as
20 exploration we're worried about cardiovascular events,
21 and it is a large molecule. A change in plasma
22 viscosity could be associated with hypertension, and

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1 certainly in cerebral vascular disease people are
2 worried constantly about viscosity and flow in small
3 vessels.

4 So I wonder if we know anything about
5 viscosity with this agent.

6 DR. WOLFSON: I'm going to call on Dr. Leo
7 Martis who is the -- or Jim Moberly.

8 DR. HIRSCH: When you come up, could the
9 question be broadened to viscosity, platelet function,
10 things that affect the rheology of blood flow? If I
11 were looking to feel better, I also want to not pay a
12 price in mortality.

13 DR. MUJAIS: The answer is clearly we did
14 not measure viscosity. So we don't have that data.

15 DR. BREM: May I make a comment?

16 I'd like to make one comment that there
17 may be a skewing or a bias for co-morbid events in the
18 Extraneal treatment group. If you look in your
19 document that you provided for us on page 61, Table
20 6(f), at baseline, if I'm reading this correctly, a
21 greater proportion of patients in the Extraneal group
22 were on agents which might suggest that they were

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1 predisposed to cardiovascular events to begin with.

2 And that may have some influence in the
3 mortality rate being somewhat higher. If you
4 preselected patients in your study group who were
5 sicker and then they had greater morbid events, that
6 might not be any surprise.

7 Specifically the issue of patients on beta
8 blockers, arenan angiotensin (phonetic) converting
9 enzyme inhibitors and cardiac therapy in general, and
10 also on anti-thrombolytic agents. So it gives you a
11 sense that perhaps this population at baseline was
12 sicker, and that may account for the differences.

13 DR. LINDENFELD: Right. Without knowing
14 more about them, without knowing some demographics, I
15 think it's hard to say because we could argue on the
16 other hand that they were on more beta blockers and
17 more ace inhibitors, and they should have had more
18 protection.

19 So without knowing, I think the baseline
20 demographics, the medications themselves would be hard
21 to help us make that decision.

22 CHAIRMAN BORER: Any other -- yes, Alan.

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1 DR. HIRSCH: I had a question about the
2 quality of life slide that was 51. That was 30
3 percent of Extraneal versus four percent of control
4 patients reported health was much better, and the p
5 was .03.

6 How many different questions were
7 considered in comparing that? I guess what I'm
8 getting at is whether a Bonfaroni (phonetic) --

9 DR. WOLFSON: No, no. That's a single
10 question. As part of the SF-36, there's a health
11 transition section, and that's sort of the lone
12 question, how do you feel compared to one year ago.
13 That doesn't fit with any of the others. so that was
14 a single question.

15 DR. HIRSCH: I didn't ask it very clearly.
16 How many questions are part of the SF-36? Is it 36?

17 DR. WOLFSON: It's 36, right.

18 DR. HIRSCH: So was a Bonfaroni done or is
19 this just --

20 CHAIRMAN BORER: Could we have the
21 microphone on down there, please? We can't hear.

22 AUDIENCE MEMBER: For those who haven't

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1 used the SF-36, it's usually reported as predefined
2 modules by Dr. Ware. So one doesn't usually
3 Bonfaroni, correct. The question is valid, but it's
4 not the custom.

5 CHAIRMAN BORER: JoAnn.

6 DR. LINDENFELD: Could you clarify for me?
7 I guess I'm switching a little bit to peripheral edema
8 here. Could you clarify for me how peripheral edema
9 was assessed?

10 On slide 43 it says zero to three was
11 recorded on the case report form, and four plus was
12 recorded as an adverse event, but then on the next
13 slide it says 17.9 percent in peripheral edema in the
14 controls.

15 So is that 17.9 percent increase in the
16 category, like from zero to one?

17 DR. WOLFSON: All of the adverse events,
18 that was the percentage of adverse events for
19 peripheral edema in each group, and it included not
20 only four plus, but all ranges of edema that the
21 investigator considered to be an adverse event.

22 DR. LINDENFELD: So 17.9 percent of the

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1 control group is anybody who had one to four plus?

2 DR. WOLFSON: It could be, yes.

3 DR. LINDENFELD: Okay, and then do we have
4 how much peripheral edema there was at baseline? I
5 guess what I want to know is did it change.

6 DR. WOLFSON: The groups were comparable
7 at baseline, I believe.

8 DR. LINDENFELD: In peripheral edema?

9 DR. WOLFSON: In peripheral --

10 DR. OGRINC: Can I comment? There's two
11 different assessments here. One is the scale that was
12 assessed as part of the physical exam at each visit.
13 That's the zero to three plus.

14 And then there's the adverse event co-
15 start term, peripheral edema. The 17.9 percent and
16 6.2 percent is percentage of patients who reported
17 peripheral edema at least once as an adverse event.
18 So it's not -- it's related to the scale only in that
19 the instructions the investigator was given were if
20 you have a four plus, make sure you record it as an
21 adverse event.

22 But they could report it for whatever

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1 reason they wanted. If they thought it was an adverse
2 event, they put it down.

3 CHAIRMAN BORER: Okay. These were
4 treatment emergent.

5 DR. OGRINC: Yes, they're treatment
6 emergent.

7 CHAIRMAN BORER: So I think that answers
8 JoAnn's question.

9 DR. LINDENFELD: And then in a similar
10 vein, you said that the dextrose patients had a 2.3
11 kilogram weight gain, and you sort of implied that
12 maybe that was because they gained more body fat, but
13 why isn't that just peripheral edema?

14 DR. WOLFSON: Well, it could be because we
15 didn't do body composition assessments during the
16 study.

17 DR. LINDENFELD: Your data suggests that
18 it is, indeed, peripheral edema and probably not fat.

19 DR. WOLFSON: It's hard. It's really hard
20 to know because, as I said, we didn't do it, but it's
21 certainly possible. Either is possible.

22 CHAIRMAN BORER: Tom.

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1 DR. FLEMING: I'm assessing, and I think
2 I've heard a confirmation from you, that you're really
3 focusing on -- when you're looking at effects on ultra
4 filtration and creatinine and urea clearance, you're
5 really looking at 130 Midas and the 035 trials, and
6 131, on the other hand, is really, is it correct to
7 say, the sole study in which we're really getting at
8 uniform assessment of survival over a year?

9 But also the quality of life assessments
10 are really all essentially coming from that trial.

11 DR. WOLFSON: Right.

12 DR. FLEMING: The SF-36.

13 DR. WOLFSON: That's correct.

14 DR. FLEMING: As well as the kidney
15 disease, quality of life. I'd like to better
16 understand the nature of the sample size here. I had
17 had it -- I don't know where this came from. There
18 was a 67 and a 62, but eventually the final sample
19 size was 175 against a control of 112.

20 Could you tell us how that basically three
21 to two balance arose again?

22 DR. OGRINC: I'll address that. The Study

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1 130 was the one month efficacy study, and that was a
2 CAPD study randomized one to one, and the patients
3 were eligible to continue into the 131 study on the
4 same treatment. They were not rerandomized, and so
5 that would give us a 50-50. There were 129 patients
6 who elected to continue.

7 DR. FLEMING: So essentially right away,
8 just to stop you at this point, there is an ill
9 defined selection factor of a third of these people
10 who drop out don't go into the follow-up 131.

11 The randomization for this cohort of 130
12 was a time zero randomization giving us 90 versus 85,
13 but then of that cohort of 175, only 100 and roughly
14 20 elected to go into 131, and their time zero is
15 still the 130 time zero?

16 DR. OGRINC: Yes.

17 DR. FLEMING: And so we, in essence, have
18 in that cohort of 131 that is made up of the 120
19 coming out of 130 some uncertainties about balance
20 because you're only capturing two thirds of the
21 follow-up into 131.

22 So then we go on from there. We've got

1 those 120 patients, and then we added to those exactly
2 whom to get the 131 cohort?

3 DR.. OGRINC: That any patient who was
4 randomized directly into 131, which would have been
5 any APD patients, they were not eligible for Study
6 130, and there may have been some CAPD patients as
7 well that did not participate in Study 130 for
8 whatever reason.

9 DR. FLEMING: So in 130 the exact numbers
10 going on treatment and control that rolled over from
11 130 are what numbers exactly?

12 DR. OGRINC: It's 129 total. I don't
13 know. Sorry.

14 DR. FLEMING: It would be interesting to
15 know. I'm trying to get at where did the excess of 63
16 come from. Was it that there was a preponderance of
17 Icodextrin patients on 130 who rolled over more so
18 than the dextrose controls?

19 DR. OGRINC: Do we have a slide on that?

20 DR. FLEMING: Because you said to get from
21 the 129 up to the 287, those additional 158 patients
22 or so were actually randomized as of new 131 patients;

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1 is that correct?

2 DR. OGRINC: Right, and they were
3 randomized two to one.

4 DR. FLEMING: Two to one. Okay. So
5 there's about on the order of 105 versus 52 or
6 something in the ones that were randomized, something
7 like that?

8 DR. OGRINC: Correct.

9 DR. FLEMING: And so there are two
10 irregularities here that we have to be aware of. One
11 is that the two sources of information that we're
12 getting come from a one to one roughly and a two to
13 one randomization. So any analysis should be
14 stratified.

15 And the second irregularity is the 129
16 rolled over from Study 130, represents only about 60,
17 70 percent of the total 130 patients, and so we're
18 using the time zero from the 130 randomization, and so
19 there's a potential bias because we've left out 30
20 percent of those randomized to the 130 trial.

21 DR. OGRINC: They're actually randomized
22 by strata, APD, CAPD, and then back size.

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1 DR. FLEMING: But that's irrelevant to the
2 selection factor.

3 At some point could you get us those exact
4 two sets of numbers?

5 DR. OGRINC: Yes.

6 DR. FLEMING: Let me go on from there.
7 I'd like to get eventually what the exact 129
8 breakdown was.

9 So essentially moving on from there, the
10 evidence that we have on the quality of life measures,
11 it would be fair to say, suggest trends, and I think
12 what you had noted on page 29 of your document is you
13 didn't call them statistically; you called them
14 clinically meaningful differences, three or four of
15 them favoring Icodextrin, one of them favoring
16 control.

17 Is it your sense, do you interpret any of
18 these data as providing compelling evidence of
19 intervention effect on direct quality of life
20 measures, or is your interpretation that these are
21 data that are suggestive of quality of life effects?

22 DR. WOLFSON: Yeah, I think the latter is

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1 how I would view this. Mr. Trotter from Ovation, who
2 carried out our quality of life assessment analysis,
3 is here, and he can probably expand upon that, but I
4 would just say that there are interesting trends here
5 that we would need to explore further.

6 DR. FLEMING: And then my final point is
7 when you do give us later on the exact breakdown of
8 the -- oh, you have it already? I was going to add to
9 the question, and that is I'd like to know where those
10 22 and 12 deaths fall into those four groups.

11 DR. OGRINC: It's 62 control and 67
12 Icodextrin patients.

13 DR. FLEMING: Okay. Sixty-seven and 62.
14 So those that are concurrently randomized must be 108
15 versus --

16 DR. OGRINC: And 50.

17 DR. FLEMING: -- versus 50?

18 DR. OGRINC: Fifty, yes.

19 DR. FLEMING: And the deaths break out
20 into those four groups in what manner? I think there
21 were 22 versus 12 when you gave us the one year
22 follow-up.

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1 DR. OGRINC: I don't know if we have a
2 table that shows the deaths broken out that way.

3 DR..WOLFSON: I don't think so.

4 DR. OGRINC: Excuse me. We have a
5 rollover.

6 DR. FLEMING: The most interpretable
7 survival data is the 108 versus 50 because that was a
8 complete cohort of concurrently randomized, time zero
9 being 131 randomization.

10 DR. OGRINC: I need the non-rollover.

11 DR. FLEMING: We can come back to that.

12 CHAIRMAN BORER: Okay. Yes?

13 DR. KOPP: I had a question about the
14 alkaline phosphatase. I know we haven't touched on
15 that before, but has that been fractionated as heat
16 labile versus heat stable, or is that coming?

17 DR. WOLFSON: It's coming. We are going
18 to discuss the rest of the adverse event profile as
19 well as some of the other data that we were hoping to
20 be able to show you. So we'll get to that.

21 CHAIRMAN BORER: Why don't we move ahead
22 to the safety profile? And when you have the

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1 information that Tom asked for, just let us know.

2 DR. WOLFSON: Can I have the slide on
3 adverse events?. Just show it.

4 Okay. Moving right along, we're going to
5 turn to a discussion of the adverse event profile.
6 There was no difference in the percentage of patients
7 with at least one adverse event, and there were also
8 no differences between the two groups in the
9 percentage of patients with at least one serious
10 adverse event.

11 I'm going to discuss peritonitis and rash
12 in a little more detail. Peritonitis was the most
13 frequent adverse event and occurred in approximately
14 a quarter of the patients in both groups.

15 Peritonitis is a very common complication
16 in peritoneal dialysis therapy, and these data aren't
17 different from overall results in peritoneal dialysis
18 patients.

19 Peritonitis was also the most frequent
20 serious adverse event, and it was serious because it
21 required hospitalization. More control patients as
22 compared to Extraneal patients required

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1 hospitalization for treatment of peritonitis.

2 Of all the adverse events only rash showed
3 a greater than five percentage point difference
4 between the two groups.

5 There's a high background rate of skin
6 events in this dialysis population, and once again,
7 skin events aren't uncommon in patients treated with
8 maintenance dialysis with end stage renal disease.

9 However, rash and exfoliative dermatitis
10 both occurred more frequently in the patients treated
11 with Extraneal as compared to the control group.

12 I'd like to point out that the term
13 exfoliative dermatitis refers to any skin event that
14 was associated with peeling of the skin, and this
15 peeling was primarily limited to the hands and feet.

16 When we look at only skin events that are
17 felt by the investigator to be related to the study
18 product, as you can see, the number of skin events
19 drops dramatically. However, there are still more
20 rash and more reports of exfoliative dermatitis in the
21 Extraneal group compared to the control group.

22 Six patients withdrew or discontinued for

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1 rash and one for exfoliative dermatitis, and all were
2 in the Extraneal group.

3 I'd like to also point out that there were
4 several patients in the Extraneal group who developed
5 a rash that was felt to be related by the
6 investigator. However, the patient continued on the
7 study and the rash resolved.

8 No patient was hospitalized for rash, and
9 all rash events in both groups resolved. There were
10 no reports of anaphylaxis and no reports of Stevens-
11 Johnson syndrome associated with Extraneal.

12 I'd like to turn now to laboratory values
13 and discuss several laboratory values that showed
14 consistent differences between the two groups.

15 Alkaline phosphatase, which was measured
16 in Study 130, 131, and the 035 APD study, was
17 consistently increased in the Extraneal group.
18 Amylase, sodium, and chloride were measured in all the
19 studies, and there were consistent decreases in the
20 patients on Extraneal compared to control.

21 Serum amylase is decreased due to assay
22 interference.

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1 So I'd like to turn now to alkaline
2 phosphatase and describe for you the changes.

3 There was an increase of approximately 19
4 units per liter for alkaline phosphatase in the
5 patients treated with Extraneal, and there were
6 slightly more patients above the normal range in the
7 Extraneal group as compared to the control group.

8 However, there were very few adverse
9 events associated with increased alkaline phosphatase
10 in either group, and there were no withdrawals in
11 either group for increased alkaline phosphatase.

12 I was going to go on and discuss the other
13 laboratory changes.

14 DR. BREM: Could I ask two questions?
15 One, was the alkaline phosphatase fractionated so that
16 you knew what it was?

17 And secondly, what constitutes an adverse
18 event with an elevated alkaline phosphatase?

19 DR. WOLFSON: Well, once again, just to
20 describe the adverse event reporting, these are
21 treatment emergent events that the investigator would
22 report on the case report form, and it might say -- in

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1 fact, all of these did say -- alkaline phosphatase
2 increased. It's usually associated with other things
3 that are occurring with the patient, but it's just
4 part of the description of the adverse event profile.

5 DR. BREM: So there wasn't a specific
6 symptom complex associated with that elevated alkaline
7 phosphatase?

8 DR. WOLFSON: No, no. It was just the
9 investigator just reported it as an adverse event.

10 DR. BREM: And getting back, was it
11 fractionated in any of the studies?

12 DR. WOLFSON: Yes, it was, and we actually
13 have Dr. DeBroe here, who is an expert, as it happens,
14 in alkaline phosphatase fractionation. So i think he
15 can take over.

16 DR. DeBROE: This fractionation was
17 performed by the classical electrophoretic separation
18 and neural amylase incubation (phonetic), which is a
19 classical one. They found 15 percent, between 15 and
20 20 percent increase of total alkaline phosphatase, and
21 the major increase was due to the intestinal alkaline
22 phosphatase; a small increase of the liver and bone

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1 alkaline phosphatase.

2 So the explanation, straightforward
3 explanation probably is, as you know, alkaline
4 phosphatases are glycoproteins. They are cyalated
5 (phonetic) or acyalated (phonetic). They have acyalic
6 acid or not.

7 Liver and bone alkaline phosphatase are
8 cyalated glycoproteins, and intestinal alkaline
9 phosphatase is an acyalic glycoprotein, which is
10 cleared very fast, very quickly from the body at the
11 acyalic glycoprotein receptor at the level of the
12 hepatocytes.

13 So the increase of intestinal alkaline
14 phosphatase suggests that there's interference of this
15 glucose polymer with the acyalic glycoprotein, and
16 there is a paper in the Journal of Biological
17 Chemistry of June of this year clearly showing that
18 glucose delavatized (phonetic) polymers are taken up
19 by the liver through the acyalic glycoprotein.

20 So it's clear that this intestinal
21 alkaline phosphatase increase is due to interference,
22 competition between this enzyme and this delavatized

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1 (phonetic) glucose polymers.

2 The major question now is is that of any
3 clinical relevance. The only clinical condition well
4 known for increase of intestinal alkaline phosphatase
5 is straightforward. It's cirrhosis because when you
6 have a cirrhosis, you have a loss of the surface of
7 the hepatocyte acyalic glycoprotein receptors.

8 On the other hand, other conditions where
9 intestinal alkaline phosphatase is increased is all
10 the drugs or proteins are interference with the
11 acyalic glycoprotein receptor.

12 So from a clinical point of view, this
13 small increase of intestine alkaline phosphatase has
14 no clinical meaning.

15 CHAIRMAN BORER: Can I just ask one
16 further question about that? You indicated that the
17 intestinal alkaline phosphatase level is increased in
18 certain disease states, presumably secondarily, but
19 does its presence in the blood cause any effects? I
20 mean, do you see bone changes because of this
21 particularly --

22 DR. DeBROE: No. The alkaline phosphatase

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1 enzymes are present in the body, and anybody has a --
2 and particularly in the renal failure patients, for
3 example, there is a slight increase already from the
4 intestinal alkaline phosphatase, but there is no --
5 the clinical biochemical effect of alkaline
6 phosphatase in the serum is nil, is nonexistent, has
7 no effect.

8 CHAIRMAN BORER: I see. So it doesn't
9 deposit itself in the bone and cause secondary
10 problems.

11 DR. DeBROE: It has to be integrated by a
12 clearance of certain enzymes interfered with
13 Icodextrin, is interfering with the clearance rate of
14 the level of the hepatocytes.

15 DR. ARMSTRONG: Jeff, I wonder if on this
16 point I could ask a related question. The sponsor has
17 given us a table of the alkaline phosphatase on page
18 82, and there is some issue about whether or not this
19 is a progressive rise, and again, we have a problem
20 with changing denominators.

21 And it looks to me as though there's about
22 a 20 or 25 percent overall increase, but the

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1 denominators change as you go through from one month
2 to one year to last visit, and I would just appreciate
3 some understanding of whether or not this rise,
4 whatever it means, is a stable, early phenomenon or a
5 progressive one.

6 DR. DeBROE: If you look to some of the
7 tables and some of the data, there is a sudden, within
8 two weeks increase of alkaline phosphatase, 15 to 25
9 percent. This increase remains stable and disappears
10 very quickly when you stop the drug, again, highly
11 suggestive for interference of the metabolism of
12 alkaline phosphatase.

13 For example, if you should think about
14 collastasis (phonetic), this is a complete other
15 picture. If you have a drug induced collastasis,
16 first of all, you have other isozymes appearing. It's
17 a liver isozyme which is appearing in the blood.
18 There is a steadily increase of liver alkaline
19 phosphatase in collastasis, and when you stop the
20 drop, the disappearance of liver alkaline phosphatase
21 is very slow. It takes months.

22 Here you have within two weeks perfectly

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1 following the plasma level, the high plasma level of
2 the Icodextrin coming down to normal values, and you
3 see exactly the same profile for alkaline phosphatase.

4 DR. WOLFSON: And this is illustrated on
5 the slide that you just put up, and this was during
6 the 035 study which had a baseline follow-up period.
7 So as you can see, alkaline phosphatase was similar in
8 the two groups. It went up within the first two
9 weeks. It remained at about the same level, and then
10 it fell during the follow-up period back to the
11 baseline levels.

12 In our 130 and 131 study, because we
13 didn't have a follow-up period after the patient was
14 discontinued from the product, we just have data that
15 shows that over the one year.

16 Can you show that slide? The alkaline
17 phosphatase in the 130.

18 As you can see, there's really no
19 difference over time. It stays fairly stable.

20 Okay?

21 CHAIRMAN BORER: Okay.

22 DR. WOLFSON: Okay. Let's continue going

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1 on then.

2 Serum sodium also declined in the
3 Extraneal patients compared to control by about three
4 millimoles. This is due to dilutional hyponatremia
5 related to the increased osmotic activity from
6 Icodextrin metabolites in the blood causing a shift of
7 water from the intracellular to the extracellular
8 space.

9 There were more patients below the normal
10 range with Extraneal, but once again, there were no
11 differences in physicians noting adverse events
12 associated with hyponatremia in either group.

13 DR. BREM: Sorry. One other question.
14 Did you actually measure the osmolality of the plasma
15 in those patients?

16 DR. WOLFSON: Yes, we did.

17 DR. BREM: And was it normal?

18 DR. WOLFSON: It was slightly elevated.
19 You know, it was in the normal range for dialysis
20 patients, but it was slightly elevated.

21 We do have a slide on that. Can we show
22 the osmolality?

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1 And this is the change in osmolality. As
2 you can see, it goes up slightly. At one month it
3 stays about the same level in the Extraneal group, but
4 it is a little bit higher in the Extraneal compared to
5 the control group.

6 Okay, and the next slide shows the similar
7 finding for chloride, which goes along with sodium for
8 the same reason and is consistent with the sodium
9 findings.

10 And finally, during our one year 131
11 study, we wanted to look at whether there were any
12 changes in peritoneal membrane transport
13 characteristics over time with Extraneal, and as you
14 can see, although there was a slight increase for
15 glucose at week 26, overall there were no differences
16 in either group for peritoneal membrane permeability
17 to small solutes.

18 So to summarize the clinical trial
19 results, I believe we've demonstrated that Extraneal
20 shows increased ultra filtration with a reduction in
21 the percentage of patients with fluid reabsorption
22 during the long dwell, and this is associated with an

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1 increase in the peritoneal clearance of creatinine and
2 urea, with also a potential benefit in preventing
3 weight gain and edema and improving quality of life.

4 The safety profile of Extraneal was
5 comparable to current therapy, and rash is the most
6 frequent related adverse event.

7 The increases in alkaline phosphatase and
8 decreases in sodium and chloride do not appear to have
9 any clinical relevance.

10 What I'd like to do now is turn over the
11 rest of the summation to Dr. Mujais, and then we'll
12 answer any other questions you might have.

13 Thank you.

14 DR. MUJ AIS: Mr. Chairman, with your
15 permission, I'd like to offer a couple additional
16 clarifications to some of the questions before I
17 proceed with the summation.

18 And the first relates to the issue of the
19 increase in viscosity. We have identified some of the
20 smaller polymers and plasma, such as maltose with two
21 glucose molecules, maltotestrose (phonetic) and, you
22 know, just slightly higher, and we find, for example,

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1 that maltose is one gram of the total five to six
2 grams.

3 Also, as we go up in the degrees of
4 polymerization to three glucose molecules, we also
5 have another gram accounted for, and as we go to four
6 glucose molecules, we have another five grams. So
7 with these small polymers that go from two glucose
8 molecules to four glucose molecules, we can address 50
9 percent of the blood levels of total carbohydrates
10 approximately.

11 So these are not very large polymers that
12 are sitting in plasma. A large proportion of the
13 total carbohydrate is the smaller polymerization
14 numbers of glucose molecules.

15 The second clarification that I'd like to
16 address relates to the alkaline phosphatase. We have
17 measured in parallel with alkaline phosphatase a
18 variety of other liver enzymes. We measured ALT, AST,
19 GGT, and we also measured bilirubin, and there were no
20 changes in any of those other enzymes.

21 And the changes that we have observed in
22 the isoenzymes for alkaline phosphatase were between

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1 three to five units for each isoenzyme of the three
2 isoenzymes that we measured.

3 So for each isoenzyme the changes were
4 very small, proportionally because the intestinal
5 isoenzyme has a smaller baseline value. That three to
6 four unit change is a percentage-wise larger change,
7 and that gave us an insight into the mechanism of the
8 increase in the alkaline phosphatase isoenzymes.

9 And finally, the other clarification
10 relates to the osmolarity issue. The change in
11 osmolarity over time by one year was around 1.4 to 1.8
12 milliosmoles (phonetic), and the decline in plasma
13 sodium can be accounted for by the effect of the
14 carbohydrate moieties. It is very similar to the drop
15 in plasma sodium that occurs with hyperglycemia, and
16 this is why we are considering this as just an effect
17 of the increased carbohydrate in plasma.

18 At this point in time, to give an overall
19 summary, we are dealing here with the population of
20 patients that has underlying very high co-morbidities
21 and where the reliance of the patients for their
22 survival and health is dependent on the ability of the

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1 dialysis process to remove fluid and remove toxins in
2 a satisfactory fashion.

3 We have identified in this population
4 problems in fluid management. These problems are on
5 the minds of nephrologists, and indeed, the
6 International Society of Peritoneal Dialysis in the
7 last two years has convened expert committees to
8 address this issue, and they have issued guidelines
9 that specifically go to the issue of fluid management
10 in this population.

11 So it is a very high issue on the minds of
12 practicing nephrologists worldwide, including the
13 United States.

14 In our clinical trials, we have compared
15 Extraneal against the solutions that are most commonly
16 used in the United States, and we find in the U.S.
17 trial that it is superior in the net ultra filtration
18 achieved versus 2.5 percent, and within the United
19 States 2.5 percent is the most commonly used solution
20 for the long dwell.

21 We also have evidence that Extraneal has
22 greater net ultra filtration compared to 1.5 percent,

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1 which is also used in some patients for the long
2 dwell, and we have a net ultra filtration effect that
3 is similar to 4.25, which we estimate is used in a
4 quarter of patients during the long dwell in the
5 United States.

6 So when we look at the summary of all the
7 dialysis solutions utilized during the long dwell, the
8 new solution is either superior or equivalent in its
9 efficacy profile and achieved net ultra filtration.

10 Finally, this enhanced efficacy that we
11 are observing with the solution versus the more
12 commonly used solutions is coupled with a safety
13 profile that except for a few aspects that are
14 specific and addressed in the label is comparable to
15 the existing solutions, and this is why we have come
16 before you with an indication or a proposed indication
17 for the solution that is shown on our final slide.

18 And that is Extraneal, we propose, would
19 be indicated for a single daily exchange for the long
20 dwell that can extend from eight to 16 hours,
21 depending on the modality the patient is using and
22 other aspects in the patient's care, and this is for

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1 both continuous ambulatory peritoneal dialysis and
2 automated peritoneal dialysis in patients who are
3 having their chronic renal failure managed by PD.

4 Now, at this point, Mr. Chairman, we would
5 be happy to address the questions.

6 CHAIRMAN BORER: I think we'll take a
7 break here until ten of four, and then when we come
8 back, we can deal with any remaining questions and
9 we'll go on to the committee discussion.

10 Thank you.

11 (Whereupon, the foregoing matter went off
12 the record at 3:38 p.m. and went back on
13 the record at 3:52 p.m.)

14 CHAIRMAN BORER: Are there any other
15 questions or issues that require clarification from
16 members of the committee before we hear from the
17 committee reviewer and then go on to the questions?

18 DR. ARTMAN: Jeff.

19 CHAIRMAN BORER: I'm sorry. Go ahead.

20 DR. ARTMAN: Everybody is sort of
21 assembling still.

22 You've presented a very compelling

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1 argument that it's really kind of counterproductive to
2 use the one and a quarter or two and a half dextrose
3 based solutions for long dwells, but then most of the
4 data you showed really compared your product with the
5 2.5 percent, with a little bit of data on the four and
6 a quarter percent.

7 And one thing I was particularly
8 interested in, and I think if I understand correctly
9 you're concluding that it's comparable to the four and
10 a quarter with regard to ultra filtration.

11 What about toxin removal? That was
12 another point that you mentioned, and I didn't see
13 those data or I missed them or something.

14 DR. MUJAIS: Okay.

15 DR. ARTMAN: Is it as effective, better or
16 worse?

17 DR. MUJAIS: We have data on toxin
18 removal, particularly urea and creatinine compared to
19 2.5 percent.

20 DR. ARTMAN: Right.

21 DR. MUJAIS: And the differential there
22 can be accounted for by the enhanced ultra filtration.

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1 So during the long dwell, the clearance of toxins is
2 directly related to the drain volume. So when ultra
3 filtration is equivalent, then the toxin removal would
4 be equivalent, and when ultra filtration is distinct,
5 then toxin removal would also be distinct.

6 So to carry this to the 4.25 equivalent of
7 ultra filtration means also that toxin removal is
8 equivalent because for these toxins that we measure,
9 it is directly related to the drain volume, and since
10 the drain volume is equivalent, then it would be equal
11 as well.

12 DR. ARTMAN: thank you.

13 CHAIRMAN BORER: Tom?

14 DR. FLEMING: A couple of different
15 questions. First, just following up on the survival
16 data, I want to come back and see if I can get that
17 breakdown of the 108 and 50. Maybe I'll start with
18 that. Do you have that?

19 The 22 and 12 would fall into these four
20 groups in what manner?

21 DR. OGRINC: Okay. First of all, the
22 table we have is the 20 and nine, which is our --

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1 DR. FLEMING: All right. I'll go with
2 that.

3 DR. OGRINC: And we have a slide to show
4 that. I just drew up a slide.

5 DR. FLEMING: Okay.

6 DR. OGRINC: The top box has the rollover
7 patients. The bottom is the non-rollover patients.
8 So those would be the patients who went right into
9 Study 131. And we see the results don't change that
10 much from the overall results.

11 DR. FLEMING: Second question, for the six
12 deaths that occurred in Diana, can you tell us how
13 many of them occurred after a year? Obviously many of
14 them did because --

15 DR. OGRINC: Yeah, most of them did.

16 DR. FLEMING: -- that's where you see the
17 curve appearing as if it's really dropping in the
18 control.

19 And as you're looking, we'll go on to
20 maybe another real quick question. In your summary,
21 you drew the efficacy conclusions that you have
22 established efficacy on ultra filtration and on

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1 creatinine and urea clearance, and in particular, as
2 well, and I assume in essence mediated through this
3 you might say, although you didn't say that, in
4 avoidance of increases in body weight and reduction in
5 peripheral edema.

6 In essence, is that what you would clarify
7 or what you would classify to be the essence of the
8 tangible clinical benefit?

9 Some, such as myself, would consider
10 endpoints such as ultra filtration and creatinine and
11 urea clearance as measures of biologic activity.
12 They're not the endpoint in themselves, but mediated
13 through those effects, we hope to achieve clinical
14 benefit.

15 And so even if one were to conclude that
16 there's unequivocal evidence of effect on such
17 measures, you're left with needing to understand the
18 reliability of the ultimate clinical benefit that's
19 achieved, and you have specifically indicated it to
20 be through edema and weight.

21 Is that essentially what you would argue
22 to be the most tangible clinical benefits?

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1 DR. MUJAIS: Let me address that with a
2 little more detail than a yes or no. The removal of
3 fluids in these patients is critically dependent on
4 peritoneal ultra filtration, and once they are anuric,
5 in the absence of peritoneal ultra filtration, their
6 survival is at great risk. So it is the function of
7 the dialytic process to remove fluid in this
8 population.

9 Additionally, in peritoneal dialysis
10 patients, their long term outcome, there are clinical
11 studies that suggest that their long term clinical
12 outcome is linked to the amount of fluid that can be
13 removed by peritoneal ultra filtration, and I would
14 like to show you one study that was published just
15 this month in the --

16 DR. FLEMING: Just as you're answering the
17 question, just to make sure we're getting at the
18 essence, it's not -- I'm not really specifically
19 asking whether it's important to achieve removal of
20 fluid, to achieve removal of waste products. It's
21 more specifically level of that removal.

22 I would characterize what we're seeing

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1 here as evidence of an enhanced rate of removal, and
2 so my specific question is: how reliable is it that
3 that additional level of -- not that we need some, but
4 that we will clinically benefit from that enhanced
5 level?

6 And let me simply say the fact that
7 there's a correlation between that and clinical
8 endpoints doesn't causally establish that we achieve
9 the beneficial clinical endpoint mediated through
10 that.

11 So what is the specific, direct,
12 compelling evidence that we have that this increase in
13 these measures is reliably leading to the conclusion
14 that we have an improvement in clinical effects, when
15 the only direct evidence that we really have about
16 this relates to edema and weight?

17 DR. MUJAIS: Okay. I think it would be
18 probably more appropriate for someone who is currently
19 in clinical practice rather than myself to address
20 this because it relates to the management of patients.

21 And if you would like, may I invite one of
22 the practicing nephrologists in the audience?

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1 CHAIRMAN BORER: Ray.

2 DR. LIPICKY: Before you do, this may
3 sound funny, but usually people without kidneys can
4 only live a couple of weeks. So the fact that this is
5 a peritoneal dialysis solution and people were on it
6 for a long time, the efficacy here is really life.

7 So the question sort of in the first
8 question you were going to address, but changed a
9 little bit, is that's really the efficacy of
10 peritoneal dialysis, life and death.

11 So the question is, I think, or let me
12 just make an assertion, and you can disagree, that the
13 efficacy of this dialysate has been amply shown.

14 Now, the question is -- the question is:
15 is there something unique about this dialysate that
16 sets it off from others?

17 So if you can accept the fact that it is
18 a dialysis solution, should it make any special
19 claims? And that is so there are a couple of levels
20 of efficacy here, and I don't know if that's what you
21 were addressing or not.

22 DR. FLEMING: Essentially the reason I

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1 clarified my own question is your first point. We can
2 accept the fact that achieving removal of fluids,
3 achieving removal of waste products is imperative. My
4 question isn't whether that is established. My
5 question is: how well do we know whether we need to
6 provide this given level of improvement in these
7 measures, and specifically if we do, how reliable is
8 it that we can conclude that moving from one level of
9 effect to another level of effect on a surrogate here
10 will reliably be predictive of enhanced clinical
11 benefit and in what way?

12 DR. LIPICKY: And that, in fact, is a
13 pertinent set of questions to something like the last
14 question here of how is it --

15 DR. FLEMING: Exactly.

16 DR. LIPICKY: -- that this is supposed to
17 be --

18 DR. FLEMING: And so I'd like to at least
19 get the sponsor's view on this answer.

20 DR. LIPICKY: Okay.

21 DR. MUJAIS: May I ask Dr. John Burkart to
22 address this question?

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1 DR. BURKART: I do not have data that will
2 show you that if I ultra filtrate 200 more mLs the
3 patient will live longer. That's your question.

4 But what I can tell you is this. We need
5 to keep these patients in neutral water and salt
6 balance so that they do not become volume overloaded.
7 As you know, if we take away access related problems,
8 the number one cause for admission to the hospital is
9 congestive heart failure or volume overload.

10 If we can keep the patient in salt and
11 water balance, we can minimize that morbid event which
12 sometimes results in mortality. I do not have direct
13 data to show you 200 mLs more will make them live
14 longer.

15 But in our current practice, keeping the
16 patients in balance is a problem. You saw that there
17 were four papers which showed that 25 percent of
18 patients have symptoms from volume overload given the
19 current armamentarium that we have to take care of our
20 patients. If we can remove the fluid, we can minimize
21 the symptoms. We can minimize the hospitalizations.
22 We can minimize the development of LVH and

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1 hypertension, which is a surrogate, we think, for
2 improving outcome.

3 DR. FLEMING: Well, you did show us direct
4 data suggesting that there was an influence on weight;
5 there was an influence on peripheral edema. Do you
6 believe their influence on many other important
7 measures, and if so, can we see these in the data?
8 And if not, why not?

9 DR. BURKART: I don't believe that this
10 study was powered or designed to try to show those
11 outcomes. It was, from what I understood, it was
12 powered in design to show that the surrogate, volume
13 removal, would be the same or better than the
14 solutions that we have available.

15 The answer do I believe as a practicing
16 physician that to be able to remove more fluid than
17 what I can with my current therapy, would that help my
18 patient, I would say, yes, I do believe that. I
19 believe there is a resistance to use 4.25 solutions,
20 and I think that the 2.5 and the 1.5 percent solutions
21 that we have are not doing the job.

22 The data that we see are for the average

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1 patients. There are subgroups even with 4.25 where
2 this solution would be markedly better.

3 DR. FLEMING: So it is correct that these
4 studies were powered to address the surrogates, and
5 they were clearly laid out to identify effects on
6 ultra filtration.

7 DR. BURKART: I believe, period. I don't
8 think anything else. I would like --

9 DR. FLEMING: And just to follow up on
10 that, they involved hundreds of patients. It's your
11 view that to be able to document what the actual
12 clinical effects are from achieving an enhanced level
13 of ultra filtration would have required much more than
14 hundreds of patients followed for six months?

15 DR. BURKART: Yes.

16 DR. FLEMING: Because the kinds of
17 measures beyond peripheral edema that we would have
18 expected to be impacted, but weren't measurable in
19 these numbers would specifically be what again?

20 Can you just quickly review what you think
21 clinically will be tangible benefits beyond those that
22 could reasonably have been identified with just

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1 hundreds of patients followed for six months?

2 DR. BURKART: Clinical benefits that I
3 would say would move me to want to use this solution?

4 DR. FLEMING: When you are saying that, in
5 fact, you believe that there are very important
6 clinical benefits that would be achieved by this
7 enhanced level of ultra filtration beyond the
8 important effects on edema that you did show, and I'm
9 asking can you describe what they would be and quickly
10 explain why it would be unrealistic to be able to see
11 even a glimmer of those effects when you're only
12 looking at hundreds of patients for six months.

13 DR. BURKART: If you're looking at medical
14 outcome data, the first one would be mortality, which
15 I think you would need many more patients to power.
16 And keep in mind that I'm saying to you these things
17 as a clinician, not as a statistician or somebody
18 that, you know, does research for my living.

19 Secondly, if a study was designed where
20 you not only were looking at ultra filtration, but
21 making sure that you monitored salt and water intake
22 in your patients, because, again, these are people who

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1 are on dialysis where we say, "You can have six
2 glasses of water a day. That's it."

3 The minute they have a solution where they
4 know shows that they're going to have more ultra
5 filtration, unless we are intervening to maintain the
6 same fluid intake and salt intake, the patients on
7 their own will liberalize their food and salt intake.

8 So it would take a study where we
9 maintained all of those things the same to be able to
10 see other surrogates, such as changed in inferior vena
11 cava diameter, changes in blood pressure control,
12 changes in left ventricular diameter or hypertrophy.

13 Many other things need to be controlled
14 that were not controlled in these studies that just
15 looked at the surrogate for ultra filtration.

16 However, I think that if I was able to do
17 that in clinical practice or in a study, if I was able
18 to control the salt and water intake in my patients,
19 that increasing the ultra filtration over time would
20 give me some of those surrogates. I think people on
21 the committee are better able to say how long that
22 needs to be studied to be able to see the changes in

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1 the left ventricle.

2 CHAIRMAN BORER: Are there any other
3 questions?

4 I'm sorry. Ray?

5 DR. LIPICKY: Just for the sake of the
6 record, I'm going to make a simplistic statement, and
7 you can disagree with it if it's too simple. But the
8 nature of this program was I am a dialysate, and I can
9 keep people alive. There was no intent to be able to
10 claim that people felt better or lived longer as a
11 consequence of some particular part of this thing, and
12 we imposed the thing of, well, but you've got to be
13 sure you don't make people sick, even though you are
14 a dialysate, because we saw examples of other
15 dialysates where they were dialysates, but they made
16 people sick.

17 And so I think the nature of the program
18 then was that, and I don't think they or anyone else
19 is trying to make something of anything different than
20 surrogate, and this business of efficacy is a very
21 tricky word because it can mean different things
22 depending on what you think.

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1 And I would reserve the efficacy part to
2 do you know people felt better or lived longer, and
3 if, in fact, we can accept the fact that it is a
4 dialysate simply because lots of people received it
5 and, in fact, they were on it for long times, long
6 enough to make all of the measurements.

7 DR. FLEMING: I don't want to pursue this
8 to an extended period of time, but it's really a
9 critical point at least for myself in understanding
10 benefit to risk. This may be one way of rewording
11 what you said, is FDA may be willing to accept this
12 surrogate as adequate in this setting, and if we can
13 simply establish an effect on this marker and it's
14 achieved with adequate safety, we are willing to grant
15 the surrogate that it's achieving clinical benefit.

16 I was trying to get a clear sense of
17 exactly what clinically we would expect to see when we
18 have not ultra filtration, but an enhanced ultra
19 filtration, and if, for example, the answer had been
20 some of these SF-36 measures, such as improved role,
21 bodily pain, general health, et cetera, et cetera,
22 then my next question is: is it really not possible

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1 that we could have been able to look at those
2 directly?

3 I always feel better if the data not just
4 show the effect on the surrogate, but also show the
5 effect on the clinical endpoint, unless we can argue
6 that the kinds of clinical effects that we really
7 expect to see here are almost absolutely certain to be
8 achieved and absolutely would require long term, large
9 sample sizes, which would then give the basis for not
10 looking at them in this setting.

11 Is that the case?

12 DR. LIPICKY: Yeah. The only exception
13 that I didn't hear you say, except the fact that it's
14 effective in prolonging life. Okay?

15 The fact that it was able to be tried
16 against two and a half and one and a half and four and
17 a half and dialyzed people for long term means that it
18 worked.

19 Now, the question is: is there some extra
20 claim that can come from some of its particular
21 properties, and would that extra claim then be a
22 specific reason to place it in a particular use or

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1 would safety be a reason to place it in particular use
2 or would just the empirical way in which the trials
3 were done place it in some kind of particular use?

4 So I think you're right on the target.
5 That is, do these surrogates tell you anything, and is
6 the measure of clinical benefit that is in the program
7 sufficient to convince you there is some particular
8 benefit.

9 But I think you have to say that you do
10 accept or don't accept the fact that this is a
11 dialysate, and that if someone wanted to use it, they
12 could, but no reason to use it other than what they
13 think in theory that, you know, some people think
14 calcium channel blockers are better than ace
15 inhibitors, even though all they do is some -- you
16 know.

17 DR. FLEMING: So if I could just follow
18 for ten seconds, then what I'm hearing from you, Ray,
19 and this makes sense to me, is clearly if it's a
20 dialysate and clearly it's providing these kinds of
21 benefits, can we say -- it's a much easier question to
22 say does it provide some efficacy than it is to say

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1 does it provide enhanced clinical efficacy relative to
2 the control group by virtue of this extra level of
3 ultra filtration?

4 DR. LIPICKY: And therefore, can there be
5 a plan.

6 DR. BURKART: Right. This is not a
7 placebo controlled indication. This is a comparator
8 trial in a sense based on superiority or equivalence.

9 CHAIRMAN BORER: Okay. Unless there are
10 some other burning issues, I'm going to ask --

11 DR. ARMSTRONG: Could I just raise -- I'm
12 sorry, Jeff, but we have hypertension reported as an
13 adverse event with excess frequency in the
14 experimental group. We've not yet heard what the
15 definition of that is and how important it is, and I
16 think that it is germane to the second part of my
17 question, which is to return to the issue of cause of
18 death.

19 The sponsor suggests that a review of the
20 narratives of patient deaths indicates that causes of
21 death were not different in the two groups. I'm not
22 reassured based on what I saw in the slide, but which

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1 is not in the documentation that that statement
2 provides me with comfort.

3 So I still need to explore a little bit
4 this issue of hypertension, what the definitions, how
5 dramatic these side effects were, and if the
6 information isn't available, surely it could become
7 available as to whether there was any relationship
8 between those findings and the apparent excess of
9 vascular deaths in the first six months.

10 DR. MUJAIS: Okay. May I address that,
11 Mr. Chairman?

12 Okay. May I have the slide that shows the
13 sitting blood pressure during the 131 trial table?

14 We have measured evidently blood pressure
15 throughout the 131, which was a one year trial, and at
16 baseline, the two groups were very similar for their
17 systolic blood pressure. I have another slide that
18 shows also the sitting diastolic blood pressure, and
19 the results are equivalent.

20 So at baseline there was no difference
21 between the two groups, and as you walk down the time
22 element for both, there is a slight difference in

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1 blood pressure at week 52 between the two groups, and
2 the difference from baseline for the control group was
3 a drop in two millimeters of mercury, and for the
4 Extraneal group, a rise of four millimeters of
5 mercury, and it is this change from baseline that is
6 reflected here in the marginal approach to statistical
7 significance.

8 But if we look at the actual values over
9 time, systolic and diastolic blood pressures during
10 this one year trial were stable.

11 Coming back to the issue of the reported
12 adverse event, these were reported by the physician if
13 they observed a change in the blood pressure in the
14 patient during therapy, and this was a double blind
15 trial. So they were reporting it, we think,
16 objectively.

17 And the difference between the two groups
18 that we report in the document is that there was more
19 than three percent difference between the two groups.
20 So it is not a very large difference that we're
21 talking about as an adverse event.

22 So this is the difference that we indicate

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1 in the document as being --

2 CHAIRMAN BORER: You know, that doesn't
3 really make everybody feel real good here.

4 DR. MUJ AIS: No, no, I will pursue it a
5 little farther.

6 CHAIRMAN BORER: Right. Because the
7 discussion we had at our last meeting regarding the
8 Allhat (phonetic) trial, at that meeting the point was
9 made that differences in blood pressure on the order
10 of what you're showing us here can be associated with
11 significant, not just important, but significant in
12 the statistical sense differences in vascular events.

13 And we saw, you know, what might be an
14 excess of strokes. Why do we see this variation in
15 blood pressure? Why do we see this pattern? Do we
16 have any idea?

17 DR. MUJ AIS: Yeah. The main difference
18 that is occurring here, what is responsible for the
19 difference is the decline in systolic blood pressure
20 in the control group rather than a rise in the --
21 significant rise in blood pressure in the Extraneal
22 group. The control group dropped their blood pressure

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1 over time.

2 We could speculate on the significance of
3 a drop in systolic blood pressure in a population that
4 has a high background of cardiovascular morbidity.

5 CHAIRMAN BORER: Well, we want to talk
6 about that. Alan and then Steve.

7 DR. HIRSCH: I mean, I just have to say I
8 have no qualms whatsoever that we have an effective
9 dialysate from all of the usual ultra filtration
10 criteria. Let's get well beyond that.

11 But, again, if we were choosing to dialyze
12 someone, regardless of merely looking at edema or
13 weight per se, I have no question that we decrease the
14 oncotic transition from the intravascular space to the
15 peritoneum. We really have seen a signal sort of in
16 the first 12 months that Tom is suggesting, that there
17 is a potential increase in vascular events.

18 The first for that, again, is instead of
19 dividing them up into a few strokes, a few PADs, and
20 a few heart attacks, that belies ever achieving
21 clinical significance. If you pool those, there
22 really seems to be to this clinician a real trend

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1 towards potential inferiority of Extraneal.

2 To boot, you've now shown us data, a small
3 sample size, but this is a product that will be used
4 in a very large population, with the kind of blood
5 pressure changes that, again, over and over again we
6 know are associated with different event rates.

7 So I'm just going to have, I'm sure, that
8 same sort of across-the-board sense that we're not
9 just seeing equivalence. We're seeing some disturbing
10 trends.

11 DR. MUJAIS: Okay. May I ask Dr. Frishman
12 to address this point, clinically, please?

13 DR. FRISHMAN: Well, again, the dialysis
14 population is different from the general hypertensive
15 population. In fact, one of the ways you can look at
16 the data also is that over time, the patients actually
17 on Extraneal are doing better because they have a more
18 stable blood pressure, have less edema, because in
19 heart failure, diastolic function, et cetera, you
20 might see a blood pressure drop along with that.

21 So you can compare, I think the general
22 population of hypertensives to a group of individuals

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1 on dialysis with fluid shifts and say that this is
2 going to be -- it may actually be representing a
3 better hemodynamic state, not a --

4 DR. HIRSCH: Well, I can't know that
5 actually. I can speculate either way, but currently
6 the data permits me to speculate as strong my
7 direction as your direction.

8 DR. FRISHMAN: Well, I just wanted to give
9 another opinion.

10 CHAIRMAN BORER: Steve.

11 DR. HIRSCH: That's nice.

12 DR. NISSEN: These are sort of coming at
13 the 11th hour here, in my view, come pretty close to
14 a smoking gun. I've got to tell you that six
15 millimeters of mercury change in blood pressure is a
16 very big change.

17 In the Hope trial, we saw three
18 millimeters of blood pressure reduction associated
19 with a major difference in long term cardiovascular
20 events. This to me is equivalent to -- you know,
21 these patients are often on multiple drugs for
22 hypertension -- this is equivalent to adding a drug or

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1 subtracting a drug from people's therapy.

2 And so I think we need an explanation here
3 of why. I don't think your explanation works for me,
4 that it's mostly driven by a reduction in blood
5 pressure in the people that were on the control agent.

6 This is a four-plus millimeter increase in
7 blood pressure in patients that were on the active
8 therapy, and I think it is very troubling.

9 DR. BREM: Okay. May I just ask? Coming
10 back to that original table demonstrating the
11 Extraneal patients were more likely to be on anti-
12 hypertensive agents at the outset, how many of those
13 patients were still on anti-hypertensive medication or
14 could I ask it a different way? Were they withdrawn
15 because their fluid balance was better?

16 So could one account for the change in
17 blood pressure by withdrawal or premature withdrawal
18 of cardiac agents known to affect blood pressure
19 because they were on an effective dialysis regime?

20 DR. WOLFSON: We did look at concomitant
21 medications. One thing that's important to understand
22 is that the reporting of concomitant medications in a

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1 group of patients who take a variety of blood pressure
2 medications and take them kind of in a self-medicated
3 fashion so that depending on their blood pressure for
4 the day, they may or may not take the medication. We
5 did not see any differences in blood pressure
6 medication changes over time.

7 One thing that might get a little closer
8 to your question about the changes in blood pressure
9 is a bar graph that we have looking at all studies
10 because that's a larger group of people. So in this
11 slide, as you can see, really overall were small
12 differences between the over time in either group.
13 What we saw though is most striking, as Dr. Mujais
14 mentioned, was that there was a large decline in
15 systolic blood pressure in the control patients than
16 there was an increase, and I think overall in this
17 overall study was about three millimeters of mercury
18 increase.

19 DR. NISSEN: This bar graph I'm sorry to
20 tell you, but it completely distorts the data. I
21 mean, you've taken on a huge scale like this, and
22 those are actually big changes. It's just that they

1 look small because of the size of the bars.

2 DR. HIRSCH: And just to sort of -- I
3 don't want to beat this too hard because reality is we
4 have an effective dialysate. I take that for granted
5 and appreciate that, and that's good for patients with
6 renal disease, but just to take it for the record, you
7 know, there are many cardiovascular diseases where we
8 give lasix, digox., and obviously separate the edema
9 manifestations from survival or event rate
10 manifestations.

11 I could speculate as easily that by having
12 these fluid shifts and bringing volume down, in fact,
13 we've been speculating here that we're activating the
14 re-enadjutant (phonetic) system, synthetic nervous
15 system, raising pressure and, therefore, causing
16 platelet aggregation, vasoconstriction, and events.

17 There's no way of knowing, but it's
18 certainly worth thinking about in the population basis
19 of the United States.

20 CHAIRMAN BORER: Okay. Ray and then Paul.

21 DR. LIPICKY: I just want to be sure I
22 know what you see. Can we see that slide of the table

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1 with difference from baseline, the first slide that
2 was shown? That one, yeah.

3 So what is it that you see there as a
4 signal? On week two control went down one millimeter
5 and Extraneal went down five and a half.

6 DR. ARMSTRONG: Did it go down, Ray? Look
7 at the hands?

8 DR. LIPICKY: Well, it says change from
9 baseline.

10 DR. ARMSTRONG: But these aren't the same
11 people, right, Ray? I mean, we start at baseline with
12 290, and at week two we have 129.

13 DR. LIPICKY: Okay, fine.

14 DR. ARMSTRONG: So I don't know that it
15 went down.

16 DR. LIPICKY: So you don't know that, but
17 then you believe that it went up four in week 52?

18 DR. ARMSTRONG: Well, but that looks to be
19 in comparable numbers. So that does look like a
20 conclusion.

21 Well, maybe just --

22 DR. LIPICKY: Well, but the week before

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1 that, I mean, week 26, it went down one. So I'm not
2 sure I see the signal that you see, and I just want
3 you to tell me which column and which row you see the
4 signal in.

5 DR. ARMSTRONG: Well, Ray, having placed
6 the fox amongst the pigeons, I'm seeing smoke at the
7 moment, and I don't know where.

8 DR. LIPICKY: Well, where is it? Which
9 row and which column?

10 DR. ARMSTRONG: Sorry. I see that there's
11 a potential trend here vis-a-vis a non-fall and maybe
12 a rise in blood pressure. I was more interested in
13 the fact that there were a higher proportion of people
14 in the experimental arm who were reported as having an
15 adverse event as defined by an excess in blood
16 pressure. That was the question I raised.

17 DR. LIPICKY: Sure.

18 DR. ARMSTRONG: And I asked the question
19 whether it would be possible since the data apparently
20 are not available at the moment, but would be
21 available, as to whether there was any relationship
22 between that phenomenon and the apparent excess in

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1 Is that what you're saying?

2 DR. ARMSTRONG: I'm saying that if those
3 deaths were not linked to people who had excess blood
4 pressure, I would be reassured.

5 DR. LIPICKY: And then wouldn't think
6 that was real or you would think that was real?

7 DR. ARMSTRONG: No, I would be --

8 DR. LIPICKY: I don't quite --

9 DR. ARMSTRONG: -- less inclined to
10 believe, less inclined to believe it was real.

11 DR. LIPICKY: Right. But, see, I don't
12 see how you can. I don't see why you looked at this
13 table --

14 DR. ARMSTRONG: Well, I looked at that
15 table because --

16 DR. LIPICKY: -- and say you saw
17 something.

18 DR. ARMSTRONG: -- because it was
19 provided. I didn't see anything in this table other
20 than the potential.

21 DR. LIPICKY: Well, because it's a table,
22 but I don't see any numbers there that tell me that

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1 vascular events.

2 DR. LIPICKY: But that was one place you
3 might find the difference --

4 DR. ARMSTRONG: Correct.

5 DR. LIPICKY: -- out of how many
6 differences were there just in adverse events?

7 So do you think that was really real? Why
8 do you focus on that?

9 DR. ARMSTRONG: I focus on that because
10 when I ask for the causes of death, there was a
11 potential link with vascular events, and we have heard
12 that there are two potentially legitimate putative
13 mechanisms.

14 DR. LIPICKY: But -- but --

15 DR. ARMSTRONG: One would be the element
16 of blood pressure.

17 DR. LIPICKY: In that set of data, there
18 have to be something different, and so then you'd say
19 if the deaths were along the lines of blood pressure
20 deaths, you'd believe that was true, and if the deaths
21 were not in the line of blood pressure deaths, then
22 you would not believe that that is true.

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1 something was happening.

2 CHAIRMAN BORER: Okay. I mean, I think
3 that --

4 DR. ARMSTRONG: Well, the denominators are
5 changing, and I'm not sure what to make of that table.

6 CHAIRMAN BORER: There are two separate
7 issues. One, is there an excess of bad events in the
8 group treated with Extraneal?

9 And you know, there's the sort of a
10 suggestion that maybe there are more vascular events,
11 but certainly that doesn't stand up -- that conclusion
12 doesn't stand up to any rigorous statistical
13 evaluation.

14 The second question is: is there an
15 excess of hypertension or a higher blood pressure in
16 general in people who have significantly high blood
17 pressure, in people on Extraneal than on the
18 comparator?

19 And I would have to say we don't know that
20 from these data, but I think it's a legitimate
21 question to ask, and no matter what else we say, we
22 might ask the FDA to request and look at those data.

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1 DR. LIPICKY: That's fine, but what I'm
2 trying to figure out is if we can go into the data and
3 say, yes, there is. What do we do with that? Or if
4 we go into the data and say, no, there isn't, what do
5 we do with that? Why do we want to do that?

6 CHAIRMAN BORER: Well, presumably if we
7 see an association with a treatment compared with a
8 standard treatment and the new treatment is associated
9 with a higher blood pressure in a way that can be
10 demonstrated statistically, then we might be concerned
11 about that because hypertension is an important risk
12 factor for vascular events.

13 DR. LIPICKY: Okay.

14 CHAIRMAN BORER: Whether or not we see the
15 events.

16 DR. LIPICKY: Okay.

17 CHAIRMAN BORER: Steve.

18 DR. NISSEN: If I can answer you, Ray, I
19 guess what I see is at every point here, the value for
20 blood pressure is higher with Extraneal than control.
21 Now, it does not reach the standard of statistical
22 significance.

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1 DR. LIPICKY: No, no, it isn't, not at
2 every point. At some of the points.

3 DR. NISSEN: Well, let's see.

4 DR. FLEMING: It is, Ray, at every point
5 basically. In a sense you're --

6 DR. NISSEN: Except for week two.

7 DR. LIPICKY: I see. I'm sorry.

8 DR. FLEMING: But week two is, in essence,
9 almost what I consider as the core starting point
10 because that's where I have the data on 62 and 67.

11 DR. LIPICKY: Okay, okay.

12 DR. FLEMING: I do see, and I grant that
13 it's not significant, but there is definitely evidence
14 here that you start with comparability in the 62 and
15 67 at around week two.

16 DR. LIPICKY: Okay.

17 DR. FLEMING: And there is an estimate of
18 a four to a six point excess. The reason that I
19 consider this relevant is if there was a relative risk
20 on mortality on the order of 1.5 or even 1.25, that's
21 a concern, to see a 25 to 50 percent increase in
22 mortality.

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1 We have no chance in this study to expect
2 to conclusively identify a 1.25 versus a one.

3 DR. LIPICKY: Right.

4 DR. FLEMING: And so what I hear my
5 colleague saying, what I think is very relevant, is
6 then look at, in essence, what clues you have in the
7 data. If there's an excess of 15 versus five in the
8 first six months, is there a pattern in the cause of
9 those deaths?

10 And if you see, in fact, that there might
11 be an apparent excess of vascular events, is there a
12 mechanism? Is there an explanation?

13 Well, if we look at the data, it's not
14 proven, but the data are suggesting a difference of
15 four to six millimeters. Is that, in fact, not a
16 potential mechanism whereby you could have achieved
17 these effects? It's not proven, but it is, as someone
18 has said, it's a smoking gun. It's a concern.

19 DR. MUJ AIS: Mr. Chairman, may I give the
20 perspective on this as far as the causes of death?
21 I'd like to contrast this with the causes of death
22 that are observed in a larger database, such as the

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1 U.S. RDS.

2 We have with us Dr. Collins, who is
3 responsible for the U.S. RDS database. Maybe the
4 information he could provide on the events in this
5 population may help the discussion.

6 DR. LIPICKY: It can't because the issue
7 is did these four millimeters make a difference in
8 these patients, not how do patients die in general.

9 DR. COLLINS: At least to the extent that
10 you've made a leap that the relationship that has been
11 shown in the general population with an elevation in
12 blood pressure and adverse events, does that same
13 relationship hold in the end stage renal disease
14 patients?

15 And the answer is no. There is no data to
16 show that the blood pressure of 140 or 150 or 160 or
17 170 is associated with an adverse mortality effect.
18 The U.S. RDS has done that study and published it in
19 a mortality and morbidity study published about three
20 years ago.

21 So the same type of relationship between
22 blood pressure that has been shown in the Framingham

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1 data and many other studies does not seem to hold up
2 in the dialysis populations.

3 that's not to say that hypertension itself
4 is not an important issue, but within observational
5 data, you cannot show the same kind of relationship
6 between blood pressure in the dialysis population.

7 What has been of a concern is the falling
8 blood pressures in dialysis patients where the
9 mortality risk is greatest when the blood pressures
10 are less than 120 millimeters of mercury. As blood
11 pressure gets lower, the mortality rate is higher, and
12 that's also been shown by U.S. RDS.

13 And so the putative mechanism there is
14 these people have a lot of left ventricular
15 hypertrophy, ischemic heart disease. As these hearts
16 fail, the blood pressures fall. We have difficulty
17 dialyzing them, et cetera.

18 So the blood pressures are actually where
19 the adverse events are associated with in the
20 observational data, not the higher blood pressures.

21 So that's why I'm a little confused by
22 making an issue of six millimeters of mercury here.

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1 If this was in the dialysis population, and it is,
2 most of the physicians would say actually that's just
3 fine. I'm not seeing a blood pressure falling, which
4 I'm much more worried about because then I can't even
5 maintain their blood pressures because they get heart
6 failure.

7 DR. HIRSCH: So let me ask you a question.
8 I feel chastened a bit because I can't say that I
9 understand the relationship of all of the things that
10 cause the high cardiac event rate in the population.
11 It's beyond the scope of today's discussion.

12 I mean, I'm aware that there's the lack of
13 clear association between high pressures and events.
14 Is not the therapeutic benefit of lowering blood
15 pressure the interventional effect the same in the end
16 stage population or not?

17 DR. COLLINS: The putative relationship is
18 it should be the same as in the general population.

19 DR. HIRSCH: Is there data that suggests
20 that that's the case?

21 DR. COLLINS: No.

22 DR. HIRSCH: In other words, does bringing

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1 blood pressure down by three millimeters of mercury
2 cause a decrease --

3 DR. COLLINS: No.

4 DR. HIRSCH: -- in cardiovascular ischemic
5 events?

6 DR. COLLINS: No, there's no data.

7 DR. LINDENFELD: Just to clarify, how many
8 patients are in your database that the data comes
9 from?

10 DR. COLLINS: One, point, one million
11 patients for the country. For these special study
12 studies, there's almost 12,000 patients that are
13 studied in these special studies for blood pressure.

14 So that's not to take anything away from
15 what you're suggesting. The data really stands on its
16 own, but in the context of these delta differences,
17 how does that relate to the population itself? Can
18 you relate the general population to these deltas?

19 The answer is I think you're stretching
20 that. It still stands on its own, the mortality
21 events and all the other stuff, but the general
22 population trends could not be applied to this.

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1 DR. HIRSCH: I'm back at you one more time
2 because the four people on this side of the table are
3 still wondering if you're going to stand by your
4 statement that this kind of lowering of blood pressure
5 in an end stage renal population is not associated
6 with benefit.

7 DR. COLLINS: That's exactly right.
8 There's absolutely no data to show that that's a
9 benefit, and in fact, the observational data would
10 suggest the opposite.

11 DR. LIPICKY: So now you take hypertensive
12 patients who have end stage renal disease and take
13 them off their meds.?

14 DR. COLLINS: Ray, I didn't say that I
15 would take them off their meds.

16 DR. LIPICKY: Well, why do you keep them
17 on if that's not good for them?

18 DR. COLLINS: Well, you know, as a
19 practicing physician, it's true that I'm trying to
20 control their blood pressures of 200, 240. Talking
21 about 140, I would be happy if I could get a blood
22 pressure of 140 in most of the patients.

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1 So I understand there's this disconnect
2 between would you not treat the blood pressure.
3 Absolutely not. But if you're looking for
4 observational data to support your hypothesis that a
5 blood pressure change of this magnitude is comparable
6 to the general population, that data doesn't exist.
7 It doesn't.

8 So I don't know what to do with this --

9 DR. LIPICKY: So now you're talking about
10 four millimeters.

11 DR. COLLINS: Well, six millimeters that
12 was discussed here. What do I do with six millimeters
13 of mercury? I don't know what to do with it. I don't
14 have any outcome studies that help me to tell you that
15 reducing the blood pressure by six millimeters of
16 mercury would be a benefit. That's my point.

17 CHAIRMAN BORER: Yeah, I don't think we're
18 going to be able to resolve this issue, but perhaps
19 what we might suggest at the end of the day is if the
20 drug is approved, that the blood pressure data at
21 least ought to be described so that people are aware
22 of the effect if they're going to use this product.

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1 And as data become available to tell you
2 how to apply the information about blood pressure, use
3 best medical judgment and best medical principles.

4 I hesitate to say any major, new questions
5 that have to be -- okay. We're going to get to the --

6 DR. OGRINC: Could I -- I've been waiting
7 to respond to Dr. Fleming's concerns about mortality.
8 Could I fit that in here?

9 CHAIRMAN BORER: Oh, yes, right.

10 DR. OGRINC: There's a train of thought
11 that I'd appreciate if you could follow with me that
12 I think addresses this.

13 In 131 study, no matter how you look at
14 it, with or without additional follow-up, with or
15 without the 130 patients in there, you see about a 50
16 percent increase in risk, relative hazard about 1.5.

17 In the non-131 study data, you see an
18 advantage in risk to Extraneal patients, recognizing
19 the possible limitations of that data. When you put
20 those two sources of data together, the overall data,
21 you have a relative hazard of 1.03.

22 So it seems to me the question that arises

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1 is when you focus on Dr. Fleming's concerns with the
2 limitations of that non-131 data, and specifically a
3 potential bias from incomplete follow-up of dropouts.

4 Now, the fortunate thing as I see it here
5 is that we have data on that to give us some idea of
6 what that might be because this was assessed in 131
7 data. We actually went ahead and got that follow-up
8 data, and what we found ere the results weren't
9 changed, but the same relative hazard with or without
10 additional follow-up data.

11 So I find that very reassuring and it
12 leads me to think that we should be focusing on the
13 overall combined data where we see no difference in
14 hazard at all.

15 CHAIRMAN BORER: Okay. Why don't we go
16 ahead then?

17 Steve, a final comment.

18 DR. NISSEN: I'm sorry to delay this, but
19 there's something I just need to understand a little
20 bit better.

21 We know that the hypertension in renal
22 failure patients is often very much volume related.

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1 What seems paradoxical about this and hard for me to
2 understand is something that's more effective at
3 removing volume ends up with a higher blood pressure
4 than something else.

5 And so I would like an explanation for why
6 something which is producing more ultra filtration,
7 presumably less edema, you know, more volume removal,
8 why is it causing the blood pressure to be higher?

9 DR. MUJAIS: May I ask Dr. Frishman to
10 respond?

11 DR. FRISHMAN: If you look at the
12 Metoprolol (phonetic) trial, heart failure study that
13 was published a year ago, they actually found the
14 blood pressure went up with Metoprolol. Heart rate
15 went down. The blood pressure went up, and it was
16 associated with a more favorable outcome.

17 So in the general population, true, you
18 know, that type of effect from a beta blocker would
19 happen. When heart failure, overall left ventricular
20 function is actually getting better, the beta blocker
21 actually will raise the blood pressure, and it's
22 associated with a favorable outcome.

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1 So I think when you have less edema,
2 perhaps less strain on the heart, the fact that the
3 blood pressure is maintained may even go along with
4 the data that Dr. Collins presented. It may actually
5 explain that.

6 So it may not be looked at as a sign of --
7 again, a blood pressure of 200 we all agree of we
8 would worry about, but this, in fact, was seen in the
9 Metoprolol heart failure trial, this three or four
10 millimeter increase in blood pressure on the beta
11 blocker.

12 CHAIRMAN BORER: Okay. We're not going to
13 get to the absolute answer to Steve's cogent question
14 today either. So let's see if we can move on to any
15 statements by the committee reviewer, Dr. Brem.

16 DR. BREM: Well, in the interest of time,
17 I will make just a couple of quick comments perhaps
18 were not made as strongly by the sponsor, and it has
19 to do with which category of approval one is looking
20 at.

21 In the past, at our last meeting reviewing
22 this drug, the committee Chairman, Dr. Packer outlined

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1 three categories, one in which the constituents were
2 perhaps altered, but there wouldn't be a meaningful
3 effect on efficacy or safety; a category two where
4 there wa sa change in the composition which was
5 significant, and it had equivalence for efficacy with
6 existing agents; and then category three where there
7 was a clear claim of superiority.

8 And I think what the company has done is
9 demonstrated a category two, that there was changes,
10 significant changes in the composition of the
11 dialysate, and they're not claiming necessarily that
12 there's a major change in efficacy.

13 However, I would say that, in fact, there
14 are subtle issues which should be at least brought up
15 for discussion, and those include the issue of
16 diabetes. A significant end stage population is
17 diabetic, and a use of this particular agent would
18 perhaps aid in the control of that diabetes.

19 Second, as a pediatrician, I'm dealing
20 with a population of children who are generally
21 categorized as high transporters, that is, they have
22 difficulty in regulating fluid balance because they

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1 absorb the sugar very quickly in the dialysate.

2 And this particular agent may have some
3 particular advantage in that population. Again, the
4 sponsors didn't provide specific study data on high
5 transporters and the increased efficacy in that
6 population, but I speculate that there probably would
7 be such data easily available.

8 The third issue is, again, a long term
9 issue which would not be addressed in a six month
10 trial, and that is related to the hypothesis that long
11 term exposure to very hypertonic solutions in
12 peritoneal dialysis may lead to a peritoneal sclerosis
13 or decrease in efficiency of the dialysis membrane,
14 the peritoneal membrane.

15 And one might speculate that using an
16 isotonic solution, such as this one under discussion,
17 may be associated with a decreased incidence of this
18 peritoneal sclerosis.

19 And the last point that the sponsors
20 really didn't discuss at all in any of their data is
21 the issue of acute symptom complex. They talked about
22 sort of global symptoms, but practitioners who deal

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1 with patients who are exposed to 4.25 percent dialysis
2 solution, those patients will frequently complain of
3 abdominal discomfort acutely because of the rapid
4 transfer of fluid that occurs that you saw.

5 And these patients will likely not have
6 that experience with this particular product. So in
7 perhaps discussing its potential significance, this
8 agent has some potential advantages over existing
9 products in those four areas.

10 Unfortunately the sponsor didn't provide
11 the data that might allow one to claim that, and
12 perhaps at some point should, and I think I will end
13 my discussion there.

14 CHAIRMAN BORER: Okay. Well, that's an
15 interesting perspective. Of course, we don't have
16 data. So we can't --

17 DR. MUJ AIS: Mr. Chairman, we have some
18 data that may be relevant. May I have your permission
19 to --

20 CHAIRMAN BORER: I'd rather you don't
21 right now. You're not making a claim. Let's just
22 deal with whether the product works and whether it's

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1 acceptably safe for its intended use.

2 Let's get to the questions then. First,
3 do the results of the clinical trials establish that
4 Extraneal is an effective peritoneal dialysis
5 solution?

6 Does anybody at the table believe that it
7 is not?

8 (No response.)

9 CHAIRMAN BORER: No. Okay. The sponsor
10 has submitted data suggesting that Extraneal is more
11 effective in removing water and in removing waste
12 products than the 1.25 and 2.5 percent dextrose
13 containing dialysis solutions, but not the 4.25
14 percent dextrose containing solution.

15 If Extraneal were to be approved, are
16 these data sufficient to support a claim of superior
17 efficacy to the existing dextrose based dialysis
18 solutions?

19 Dr. Brem, why don't you deal with that, if
20 you would?

21 DR. BREM: Let me just get my right copy
22 here. I have three copies of the same question list,

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1 and it looked like they were all different.

2 CHAIRMAN BORER: Remember the lower right-
3 hand corner of the front page will say August 8th.
4 This won't.

5 DR. BREM: I don't think they have data to
6 suggest superior efficacy against 4.25 percent.
7 Obviously they're not claiming that, but they are
8 claiming superior efficacy over the dialysis solutions
9 most frequently employed for long dwells. I think
10 they can make that claim.

11 CHAIRMAN BORER: Does everybody agree with
12 that? Are there any other comments?

13 DR. LIPICKY: Does he mean efficacy or
14 that it affects a surrogate more?

15 DR. BREM: Well, the surrogate marker is
16 ultra filtration, net fluid removal, and I think they
17 have data that will support the statement that against
18 the most frequently used dialysis solution
19 concentration there is increased efficacy.

20 DR. LIPICKY: That they affect that
21 surrogate more.

22 DR. BREM: The surrogate is fluid removal.

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1 CHAIRMAN BORER: Yeah, the issue is
2 clinical efficacy versus pharmacological effect
3 basically, and we see that there seems to be more of
4 a measurable, if you will, pharmacological effect. I
5 don't know that we have any data to say that it's more
6 efficacious, that is, it keeps people alive longer,
7 all the points that Tom was making.

8 So the question is: can we say from these
9 data that the product is more effective than the
10 comparators as a clinically beneficial therapy, or can
11 we only say that it -- or can we say that it has more
12 of an effect on a measure of pharmacologic
13 effectiveness, I suppose, but we can't say that causes
14 enhanced clinical benefit?

15 DR. BREM: Right. I think, yes, I
16 misunderstood the question. I believe that it has
17 equivalence of existing solutions in terms of
18 efficacy. It has pharmacologic benefit over the most
19 commonly used solutions for long dwell currently
20 employed by clinicians.

21 CHAIRMAN BORER: Okay. So I think that
22 the answer is we can't say it's more effective, but it

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1 does have certain different effects -- effects on
2 certain measures that are greater than the standard
3 solutions.

4 If not, what might be required for
5 dialysis solution to claim superior efficacy? And I
6 think that Tom really discussed that at length
7 earlier.

8 In Study RE97CA131, the sponsor measured
9 changes in patients' symptoms using three different
10 instruments: the KDQOL, short SF-36, and the global
11 assessment of QOL. From these data, what can you
12 conclude about the effects of Extraneal on symptoms
13 compared to dextrose containing dialysis solutions?

14 Dr. Brem?

15 DR. BREM: I don't think you can really
16 say anything.

17 CHAIRMAN BORER: Okay. Does anybody
18 disagree with that?

19 (No response.)

20 CHAIRMAN BORER: No. Icodextrin is
21 absorbed systemically. Are the data on the absorption
22 distribution metabolism of Icodextrin sufficient to

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1 describe them in labeling?

2 JoAnn, you discussed that at some length.
3 What do you think?

4 DR. LINDENFELD: I think probably that we
5 have enough data to talk about that. I don't think we
6 know anything about effects on viscosity, and I think
7 just in coming back to this that there are likely to
8 be substantial effects. I think the concentration
9 that was described is similar to fibrinogen, but I
10 think just of the molecule itself, I think, yes, we
11 have that data.

12 CHAIRMAN BORER: She's saying that we do
13 have enough information to describe the effects in
14 labeling, though there are some other effects one
15 might like to know something about.

16 Are the data sufficient to explain any
17 pharmacodynamic or clinical effects that might be --
18 I can't read the word here.

19 DR. LIPICKY: Of concern.

20 CHAIRMAN BORER: Of concern. Okay.
21 Sorry.

22 DR. LIPICKY: Let me interpret the

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1 question. Since this is absorbed, fundamentally
2 Icodextrin can be regarded and should be regarded as
3 a new chemical entity. Is the smoking gun of
4 hypertension related to it? Is the exfoliated
5 dermatitis related to it? Are any of the other
6 things?

7 So that it's sort of does any of this tie
8 together by what you know from the pharmacokinetics or
9 pharmacodynamics, or are these things just sort of
10 happening?

11 CHAIRMAN BORER: Okay. Steve.

12 DR. HIRSCH: In other words, if we infuse
13 this medication in normal volunteers to comparable
14 plasma levels, what would happen to blood pressure?

15 DR. NISSEN: Well, that is exactly what I
16 was going to say. I don't think we know, but I think
17 that there is a suspicion here that the systemic
18 absorption of this agent is leading to moderate
19 elevation of blood pressure.

20 And I must tell you I don't buy the
21 argument that it's making the heart work better and
22 therefore the blood pressure is going up. I just

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1 think that that's very, very weak logic.

2 And therefore, the only conclusion that I
3 can come to, Ray, is that there's something going on
4 here with this agent in the systemic circulation that
5 may be responsible for blood pressure.

6 DR. LIPICKY: This is just glucose.

7 DR. LINDENFELD: No, it's not glucose
8 until it's broken down to glucose.

9 DR. NISSEN: You know, I think that that's
10 a plausible explanation that would require, I think,
11 subsequent surveillance and care.

12 CHAIRMAN BORER: Okay. So the answer then
13 would be, no, we don't know. The data are not
14 sufficient to explain any pharmacodynamic or clinical
15 effects that might be of concern.

16 Are there sufficient data to conclude that
17 Extraneal is a safe peritoneal dialysis solution with
18 respect to mortality?

19 Tom?

20 DR. FLEMING: Well, this is certainly a
21 very difficult issue partly because realistically I
22 would assume the plausible kinds of adverse effects

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1 aren't a doubling or a tripling in mortality. They're
2 probably more subtle and yet still could be very
3 important, 25 percent increase, 50 percent increase.

4 And these data -- a study that essentially
5 -- a summary of data that involves roughly 600 people
6 is not going to be able to reliably sort out the
7 distinction between no increase and a 25 or 50 percent
8 increase.

9 It's my sense that the best data that we
10 have are in studies where we have uniform follow-up of
11 patients over time, and in essence, that really is
12 provided by these 297 patients who are part of the 131
13 assessment, which as Peter pointed out are essentially
14 made up of two cohorts, both of which have a relative
15 risk of about 1.5.

16 That's what we have when we look at the
17 totality of these data. So those data certainly in
18 their own right are suggestive, but by no means proof,
19 but suggestive that there could be an increase.

20 When we break down the pattern of events
21 over time, what we see is over the first six months
22 where there is probably the best uniformity of follow-

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1 up and where the effects might be most clearly seen
2 because you're looking at a contrast between the
3 Icodextrin and control groups that are more sharply
4 maintained over that first six months, their 15 deaths
5 versus five and there's an apparent excess of vascular
6 events.

7 And we've had a lot of discussions about
8 the blood pressure changed possibly being a smoking
9 gun, and is a four or six millimeter difference
10 important, and we're hearing maybe not so much as it
11 would be in a broader population, but if we had an
12 increase in the number of people with really high
13 levels, that would be a concern.

14 I don't know if we do or don't. I know
15 that the average is increased by six. It might be
16 that in the tale there is actually also an increase in
17 the fraction that have high levels.

18 I think it would certainly be worthwhile
19 for the FDA to do further explorations of this, and
20 I'd be interested in hearing my colleagues' comments
21 on what they think might be plausible ways of doing
22 this in a realistic way using the kinds of data that

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1 we could readily get.

2 One approach to this would be to explore
3 more carefully what the entire distribution is in
4 blood pressure, not just what the means are, to see
5 whether there is a difference in the tale and if
6 there's any suggestion of a relationship with the
7 nature of the deaths that are occurring.

8 Peter O'Brien made the comment that when
9 we did go back and get more uniform capture of follow-
10 up in 131, those additional deaths that we saw didn't
11 show an excess, and that seems to be correct, although
12 it's in small numbers. So it's unclear whether that
13 means we can reliably say that the data we don't have
14 on follow-up in the other trials wouldn't show, and
15 also I don't know whether what is true in one study
16 applies to another study.

17 So there are also then possibilities
18 without having to do new studies of being able to get
19 much more data from the current studies that are the
20 source of the information for mortality, to see
21 whether or not with more complete mortality data these
22 trends that are definitely there, but aren't proofs of

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1 increases, but are worrisome are exacerbated or
2 attenuated, whether or not we can take also more
3 reassurance as you look at the cause of these deaths,
4 if you can get that information as to whether or not
5 there is an indication of an increase specifically in
6 vascular events or other types of events.

7 If these kinds of results are
8 inconclusive, then certainly an alternative here is to
9 look at exploring need for additional studies, but I
10 think at this point what I'd like to hear is comments
11 from colleagues before I comment any further on this.

12 CHAIRMAN BORER: Can I ask you, Tom?
13 You've discussed what assurances might be useful or
14 appropriate, but looking at the data as you have them
15 and knowing what population this treatment is meant
16 for and knowing that it is effective to the extent
17 that it is, is this a major factor that would bar
18 approval in your opinion, or is it something that can
19 be for the moment dealt with with a description in
20 labeling?

21 And let me before you ask that throw out
22 sort of a simplistic suggestion. I'm not sure in view

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1 of the discussion we've had here that we know what to
2 do about the variation in blood pressure, but let's
3 say we think we did, and we think that the appropriate
4 response is to lower it.

5 If we give somebody a dialysate and we
6 take the blood pressure and we think it's too high and
7 we think it's too high the next time we measure it,
8 presumably we free to do something else to get the
9 blood pressure down the way we would with anyone who
10 wasn't being dialyzed.

11 So keeping that in mind, is it sufficient
12 to describe the issue in labeling or do we have to
13 disapprove the agent because we have that concern?

14 DR. FLEMING: Well, I would for the most
15 part turn that question back to you and to colleagues.

16 CHAIRMAN BORER: Okay.

17 DR. FLEMING: Is the risk of a mortality
18 increase here unacceptable? In turning it back, let
19 me say that my anticipation is if you knew for a fact
20 that there was a 25 to 50 percent increase in
21 mortality, you'd probably consider that unacceptable.
22 That's my anticipation of what you would say.

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1 On the other hand, if we were required to
2 rule out 25 percent increases for all kinds of
3 interventions in this setting, we'd have to do studies
4 that would target 600 deaths. To rule out even a 50
5 percent increase is going to take studies that would
6 require on the order of 150 deaths.

7 These will be very large studies. My
8 sense is we typically would require those only when
9 there is a reason to anticipate either from data that
10 we see or understanding of mechanisms of action that
11 it's plausible that there could be an increase, and so
12 essentially what I see in these data is a suggestion
13 over the time period where I have the most confidence
14 in the quality of data that maybe there is a 50
15 percent increase in the death rate, but that's highly
16 nonconclusive, and longer term data seem to offset
17 that, although the longer term data I have some
18 concerns about because of irregularities in follow-up.

19 And so what I would say when I look at
20 this then is are there other factors that make me
21 believe that these trends that are very inconclusive,
22 but worrisome if they were real, are in fact

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1 potentially real.

2 CHAIRMAN BORER: Okay. Steve, is this a
3 major factor that would bar approval or is it simply
4 a labeling issue?

5 DR. NISSEN: I don't think it's a major
6 factor that ought to influence approval, but I think
7 that perhaps ought to influence what kind of post
8 marketing surveillance is performed or required here.

9 And, again, there is just enough
10 discomfort here from the things that we've seen on the
11 mortality side and the blood pressure side to want to
12 know more.

13 Now, what form should that take? I don't
14 know that I'm prepared to describe that, but it seems
15 to me that, you know, since at least historically in
16 cardiovascular medicine -- you know, I know your data
17 is kind of to the contrary -- you know, high blood
18 pressure is not a good thing, and I worry about what
19 Tom worries about, is if you see a six millimeter mean
20 increase, out at the tail are there people who are
21 getting up in that 200 range that wouldn't get up
22 there if they weren't on this agent? And are those

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1 people going to have CVAs?

2 And so I guess I think we really should
3 recommend -- I believe we should recommend an
4 appropriate post marketing surveillance program or
5 maybe even some Phase IV studies designed to improve
6 our understanding of this blood pressure and mortality
7 risk that may be associated here.

8 CHAIRMAN BORER: Ray, I'd like to ask for
9 a clarification here if I may. We have here an agent
10 that is a dialysate, as you've defined it, as you've
11 defined a dialysate, which means that whatever it may
12 do in terms of mortality risk versus 2.5 percent
13 glucose, it's a heck of a lot better than not
14 dialyzing somebody.

15 DR. LIPICKY: Right.

16 CHAIRMAN BORER: There are some potential
17 advantages that have been described, maybe some
18 quality of life issues. Maybe they're not advantages.
19 May there are some detriments here, although as Steve
20 pointed out, the data in his view and in my view, too,
21 don't constitute a bar to approval, but do constitute
22 a labeling issue and maybe a requirement or a request

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1 for additional follow-up data.

2 Is it necessary that we use as a standard
3 that we can or cannot show that this agent, which is
4 certainly better than not dialyzing somebody, is
5 materially or significantly different from a standard
6 that's already on the market?

7 DR. LIPICKY: Well, we're asking you for
8 that advice.

9 CHAIRMAN BORER: Okay. That's fine.

10 DR. LIPICKY: But let me amplify on that.
11 I think the issue here is that you know it's better
12 than nothing, and so this business with blood pressure
13 and excess cardiovascular mortality is clearly a
14 fringe that may be along the lines of ultra
15 filtration, if you will.

16 And you clearly said we're not going to
17 let anybody say ultra filtration is very important.
18 So I think there's a judgment.

19 CHAIRMAN BORER: Okay.

20 DR. LIPICKY: This is a judgment call, and
21 that's why "safe" is in quotes.

22 CHAIRMAN BORER: Okay. That's a fair

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1 enough clarification.

2 Let's go on to --

3 DR. ARMSTRONG: Can I suggest, Jeff,
4 before you left this then --

5 CHAIRMAN BORER: Yes, sir.

6 DR. ARMSTRONG: -- that as I understand
7 it, there are two pieces of data in hand by the
8 sponsor, but not at hand for discussion today. One is
9 a box plot of the blood pressures so we could see the
10 outliers, and two would be the identification on that
11 box plot of where the patients with cardiovascular
12 death exist; that that would be a simple declaration.

13 DR. LIPICKY: Well, we can get that, and
14 we'll use our best judgment as to how to interpret it.

15 DR. ARMSTRONG: Right, and the third piece
16 would be at some point, whether it be now or soon, I
17 think this issue of measurement of viscosity as a
18 potentially legitimate mechanism for hypertension and
19 a potential factor in some of the discussions needs to
20 be done.

21 CHAIRMAN BORER: Okay. The committee then
22 recommends that these issues be pursued irrespective

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