

1 steroids according to an algorithm that people would
2 flare.

3 So I know I was one of the people who was
4 very much surprised to learn about this data that the
5 people with SLEDAIs of 2 or less were different than
6 the people with SLEDAIs of greater than 2.

7 So I think, you know, it's nice now to say
8 that we should have made these definitions and these
9 guesses, but that's one of the reasons we have the two
10 outcomes we do for 94-01, and I don't think we could
11 have prospectively back then guessed about a SLEDAI
12 score, because we didn't understand the instrument.
13 We had never used it in a clinical trial, and it had
14 been used really only in certain cohorts.

15 ACTING CHAIRMAN HARRIS: Thank you very
16 much. I guess, again to repeat, we are very much
17 feeling our way along here, because this is so new,
18 and you know, given the effort, the discussion that
19 must have gone into it dealing with territory that was
20 uncertain and, I think, setting parameters that might
21 be scientifically meaningful, I mean six/seven years
22 after the fact, you know, I think one may -- Really,
23 what I do hope -- I think what is hoped here is that
24 today dealing with one particular drug, one particular
25 trial developed sometime ago, I'm hoping, too, that we

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1 can get some lessons from this particular trial that
2 are certainly going to guide us as we move along,
3 because there are certainly going to be more trials
4 along the way.

5 Of course, the trouble is that we do have
6 to decide whether there is scientific data to support
7 the efficacy of this particular agent in patients with
8 lupus, which -- you know, sterile is necessary for the
9 Committee.

10 Okay. Let me go to the third question.
11 In study 95-02 the sponsor amended the original
12 protocol and defined the per-protocol analysis to
13 include only those patients who completed 60 days of
14 treatment and had measures recorded after that time.
15 Such a definition may exclude information regarding
16 drug effect, particularly related to toxicity/safety.
17 Please comment on the clinical relevance of results
18 that are based on such a per-protocol definition.

19 Of course, we have had some discussion of
20 this from both sponsor and FDA this morning. I am
21 going to start perhaps with the statisticians.

22 DR. ELASHOFF: Personally, I think that
23 the major analysis that one pays attention to has to
24 be the intention to treat, that it is -- although it
25 might make sort of logical sense to say, well, I only

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1 want to look at people who have completed a certain
2 number of days of treatment, the important thing is
3 how does a person that we attempt to give this
4 treatment to do, and for that you have to go back to
5 how things are randomized, especially in a situation
6 where people drop out due to adverse events and that
7 sort of thing, and you are never entirely sure exactly
8 what reasons they dropped out, plus why 60 days? Why
9 not 50? Why not 80 or 90?

10 It seems to me completely arbitrary. So
11 I would be opposed to putting one's major attention on
12 such a per-protocol analysis.

13 DR. TILLEY: I agree.

14 DR. ANDERSON: I don't have anything to
15 add to that.

16 ACTING CHAIRMAN HARRIS: I'll turn to the
17 clinicians. Dr. Liang.

18 DR. LIANG: Well, I know it's statistical
19 malpractice, but -- But in clinical practice I
20 wouldn't give up on a new drug until they have been on
21 it for a while, even -- I mean especially this kind of
22 a drug. I mean, prednisone, I would expect to kick in
23 almost right away, sometimes up to a week. But I
24 think, you know, we basically marry our patients when
25 we see them, and you don't want to eliminate something

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1 right off the bat. You know, you're going to have to
2 deal with this again. So I like to -- especially if
3 the toxicity is not so bad. Let it hang in there for
4 a while and sort of see.

5 So I don't think clinically it's out of
6 line. In fact, most of the drugs that we use besides
7 prednisone, we wouldn't abandon after 60 days, I don't
8 think.

9 DR. WILLIAMS: I think there's value in
10 both evaluations, and we often did that in RA studies
11 in that we would report the intention to treat, which
12 is the clean way to do it, but then you want to know
13 what happens to the patient that continues to take the
14 medication, that can tolerate it and continues to take
15 it.

16 So I think that there is a place for both
17 of them, but I think I would have to agree with the
18 statisticians. The primary one has to be the
19 intention to treat, but I'm also interested in those
20 who stay on the medication.

21 DR. FIRESTEIN: Yes, I agree with all
22 those points. The other question has to do with the
23 issue of do you use the cutoff at 60 days, 50 days,
24 how do you determine that.

25 It seemed to me, although I wasn't privy

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1 to all of the early discussions on this, that that was
2 selected as a time point where it was not thought that
3 -- it would take at least two months to see efficacy
4 of the drug, but it's not clear what that's based on,
5 if there hasn't been a study that demonstrates
6 efficacy.

7 So in other words, how do you know that it
8 takes 60 days to see drug efficacy if you haven't
9 demonstrated efficacy yet?

10 DR. VAN VOLLENHOVEN: Maybe I can just
11 make a quick comment on that. If I may, Mr. Chairman,
12 I would just like to comment on the Stanford study.
13 That was the first controlled study with DHEA in 28
14 lupus patients, and there we had followed patients
15 monthly, and during this three months that we did the
16 follow-up in double blinded fashion, we did see
17 increasing efficacy parameters.

18 That is to say, we saw that there was a
19 divergence between the patients on DHEA and placebo
20 that increased to the point where at three months
21 there was a clear separation.

22 As Dr. Petri discussed, it was in some
23 instances statistically significant or nearly. But
24 there was a clear difference between those results
25 after three months as opposed to one or two months.

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1 DR. FIRESTEIN: I understand that, but
2 that study is not a study that is really up for
3 evaluation. It's not one that is potentially
4 approvable. There is no -- They can't be used to
5 prove that the drug is effective within 60 days, if
6 it's going to be working or not.

7 So again, I think there's a lot of
8 arbitrariness that goes into the decision to choose 60
9 days.

10 DR. GURWITH: Just to clarify, that's how
11 the 60 days was chosen, was based on Ron's study. It
12 was actually partly in the initial protocol, because
13 we had this complication definition of clinical
14 deterioration which was part of the initial original
15 analysis plan, which took account of 60 days; because
16 in terms of the steroids, how much steroid the patient
17 had to receive to be considered a clinical
18 deterioration.

19 So it was present right from the beginning
20 of the study.

21 ACTING CHAIRMAN HARRIS: Okay. I'm sorry,
22 Dr. Brandt.

23 DR. BRANDT: Yes. I think fundamentally
24 I have to side with the statisticians. As a
25 clinician, I have no problems with a drug whose onset

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1 isn't for 60 days. That doesn't bother me one iota,
2 but I think that if I were a physician prescribing
3 this drug or if I were a patient making a judgment
4 should I take this drug or not, I want to know what to
5 expect in those first 60 days both with regard to
6 toxicities and with regard to efficacies in making
7 that decision.

8 If I should have the expectation that it
9 is not going to work for 60, that's okay, but I think
10 that those data -- As a secondary analysis, that may
11 be fine, but I think it can't replace, in my judgment,
12 the ITT as a primary.

13 DR. WILLIAMS: The problem I have with
14 this protocol analysis. It's just the 60 days of
15 drug, and then they could have stopped the drug at Day
16 61 or 62. I think, if you are going to have -- I
17 think you need an intention to treat.

18 Then the one study I would want to know is
19 those who completed the trial on the drug rather than
20 those who just took it for 60 days.

21 DR. SILVERMAN: The question is really
22 coming back to clarification also. I did not in depth
23 review the initial study, but if I understand what was
24 just said, you were beginning to see a response at 30.
25 The response was more at 60, and was almost

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1 statistically significant at 90. Is that what you
2 said, Ron? That is what I heard, which is completely
3 different than saying there is no response until 60
4 days.

5 I would use the analogy of methotrexate
6 where we see response at six weeks, but it may not be
7 maximal at six weeks, and are we hearing the same
8 thing here? That's what Ron said. Now he can be
9 corrected, but that is what I heard.

10 DR. PETRI: But may I clarify, because I
11 think the misperception is in thinking of the per-
12 protocol population as a two-month population. In
13 fact, a difference between the per-protocol and the
14 ITT is really the 32 patients who had no post-baseline
15 measures.

16 There are only three patients in which the
17 60-day rule had any effect.

18 DR. SILVERMAN: But it was a 90-day rule
19 then, because they've missed their 90 days. So let's
20 say it's a 90-day rule, for argument's sake.

21 DR. PETRI: But those 32 patients had no
22 post-baseline --

23 DR. SILVERMAN: Which is 90 days, though.
24 Your first measurement was at 90 days.

25 DR. PETRI: There is no way to either

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1 evaluate response or clinical deterioration or
2 anything in those 32 patients. They had no post-
3 baseline measures. So there are only three patients
4 here in which the two-month issue is even relevant.

5 DR. SILVERMAN: I just want to answer my
6 question. So, in fact, this 60 days is arbitrary,
7 because you do see response at 30. You do see
8 response at 60, taking Dr. Petri's comments into
9 account.

10 DR. TILLEY: Just in general in a clinical
11 trial, it is traditional that you expect some
12 proportion of dropouts, and then you power your sample
13 size such that you can tolerate those dropouts. So I
14 mean, you don't just ignore them.

15 ACTING CHAIRMAN HARRIS: I think that
16 there seems to be a consensus around the table with
17 respect to the use of ITT as a basis on which to go
18 ahead, but of course, from a clinical perspective, you
19 know, some of us feel edgy. You know, maybe we should
20 consider some of the data, the other data, despite
21 that.

22 I don't know how you may call this one way
23 or another, but hopefully, you got the sense of it.

24 DR. JOHNSON; Well, let me put a question
25 back to you. What if you looked at this from two

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1 different conceptual points of view, and that is you
2 use the ITT to make a call as to whether or not drug
3 works, and you use some other minimal duration
4 exposure to determine if you've got a durable drug
5 effect. And those are separable concepts.

6 This sort of comes up with longer term
7 trials is why I bring it up.

8 DR. SILVERMAN: The other issue is also on
9 practice. If a patient stays on the drug, it is also
10 clinically important. So my point is, for whatever
11 reason patients don't take it for 90 days, those that
12 do take it for 90 days I want to know about.

13 So it becomes a different clinical issue.
14 So one can report -- slightly different from what Kent
15 is asking -- but you can report two ways. One is if
16 they take a whole population -- My ITT population, it
17 didn't seem to affect. But if the patient continues
18 on the drug for 90 days or durability, then it's a
19 useful drug, and that is what the data seems to show.

20 So you do have patients who don't take the
21 drug, for whatever reason, drop out early, but those
22 patients who stayed on it appeared to respond. So
23 there are two useful pieces of data.

24 DR. FIRESTEIN: I think it depends why
25 they stopped taking it. I mean, if they stopped

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1 taking it for toxicity reasons, then it's not clear
2 that that would hold up.

3 DR. GURWITH: Could I once more just try
4 to explain?

5 ACTING CHAIRMAN HARRIS: Make it brief.

6 DR. GURWITH: I'll be very brief. The
7 intent to treat population is patients who -- all
8 randomized patients. We defined a per-protocol
9 population, but it is common to have a modified intent
10 to treat where you have to deal with patients who
11 don't have any post-baseline measurements.

12 Our per-protocol is very close to that and
13 gives very similar results. So the real issue is what
14 to do with patients who didn't have any post-baseline
15 measurements. Many of those left the study way before
16 90 days. Some of them left the study after 90 days.
17 They just didn't get back to their visit.

18 So we do actually, in the intent to treat
19 population, have information on patients who were
20 treated -- who came within even under 60 days, and
21 they are included in the modified intent to treat
22 patients. Those are those three patients.

23 ACTING CHAIRMAN HARRIS: I am almost
24 tempted to go around the table and ask for an opinion
25 on this. But -- Yes?

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1 DR. VILLALBA: I just have one point, in
2 that some of those patients who were not included in
3 the analysis had dropped out because of adverse
4 events. So there was some biological activity
5 detected before 60 days, regardless of there was no
6 efficacy measurements.

7 ACTING CHAIRMAN HARRIS: You know what?
8 I am going to go around the table and ask or you don't
9 think that is necessary? I think we have a consensus
10 here. Okay.

11 DR. BULL: Excuse me. Would you just
12 clarify the consensus?

13 ACTING CHAIRMAN HARRIS: Okay. I think
14 most people feel it is important that we use the
15 intent to treat, you know, in terms of the analysis
16 that we did. I think that is the consensus. Is that
17 true? Any objectors? Yes?

18 DR. SILVERMAN: But you also look at both.
19 I understood the consensus to look at both.

20 DR. WILLIAMS: But there's also value in
21 looking at the per-protocol to see how many of the
22 people stay on the drug, and I'm not sure that what
23 this analysis in this trial was is that same thing
24 that we are talking about; because these were just
25 people that took two months' worth and then they could

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1 have stopped, where I think there's value for those
2 who continue to take the drug. That's also of value.
3 I'm not sure this protocol did that.

4 DR. LIANG: I am actually -- I'm hearing
5 two different questions. I mean, one is Kent's one
6 comment. You said, well, what are we going to use to
7 answer the question does this thing work --

8 ACTING CHAIRMAN HARRIS: Yes.

9 DR. LIANG: -- for licensing, I assume.
10 Then we are talking about what we like to see in the
11 tables, because we are sophisticated customers. I
12 think we haven't answered your question necessarily,
13 and I would take a run at it.

14 I would try to make a distinction between
15 effectiveness studies and efficacy studies. You know,
16 this is a new drug with imperfect methodology, and I'm
17 more persuaded, I think, by the people who had a fair
18 go at the drug, because if the toxicity profile was
19 horrendous clinically, I would be really nervous. But
20 I think these are things that I could live with as a
21 clinician.

22 So I would rather take the people who are
23 able to stay on it for a reasonable go, realizing that
24 hormonal therapy doesn't work, you know, in 48 hours,
25 and to assess whether the thing has an effect. That's

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1 my opinion.

2 ACTING CHAIRMAN HARRIS: So, Matt, how
3 would you advise -- Suppose you are advising -- I
4 mean, let's frame this into something that I can ask
5 around the table that people might -- Yes or no? I
6 mean, how would you frame a question there or a
7 recommendation?

8 DR. LIANG: Which endpoint would you weigh
9 the most to answer the question does this thing work?
10 Does this drug work? Isn't that what you asked us?

11 DR. JOHNSON: Which analysis, really. I
12 mean, if you opt for the second analysis, the per-
13 protocol analysis, you are going to have to give us
14 some statistics to use, because classical statistics
15 are invalidated if you don't use the all-randomized
16 subset -- really all-randomized set. So that is, in
17 some sense, a secondary question.

18 ACTING CHAIRMAN HARRIS: Any other
19 comments, statisticians? You were pretty clear in
20 terms of your view. Okay.

21 Do you feel as if this discussion has been
22 sufficient in terms of giving you guidance about how
23 we might move along? Yes?

24 DR. BULL: I was just wondering whether or
25 not the committee might -- I'm sort of not hearing

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1 response regarding the part of the question where such
2 a definition, if you go by the per-protocol analysis,
3 makes good information regarding drug effect,
4 basically informative censoring. But you could relate
5 it to toxicity and safety. I would just like for you
6 all to revisit that part of the question for us.

7 DR. FIRESTEIN: Yes. Actually, I think I
8 did comment on that, that I think that that is a
9 potential serious problem. I completely agree with
10 the -- The question is, you know, if you look out, you
11 know, three months, six months, are our patients going
12 to be continuing on it and responding. But if a
13 quarter of the patients are dropping out in the first
14 three months, that is -- particularly because of
15 either toxicity reasons or whatever, then that is
16 going to be critical in terms of deciding whether or
17 not the drug has biological effect and has a favorable
18 risk/benefit ratio.

19 DR. SILVERMAN: And I would just -- If you
20 go back -- I mean, my comment was just, when I looked
21 at the adverse event data which was shown to us on
22 those patients who did drop out, it was mainly acne
23 and hirsutism. So I was basing my comment on a
24 nuisance side effect.

25 So I can tolerate in patients -- I have no

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1 problem -- If that's true. So I think the answer to
2 the question is one would have to look at the adverse
3 event data on every single dropout and, if the
4 assumption is there is no serious adverse events
5 beyond nuisance adverse events, then I'll stay by my
6 comment, knowing -- But, obviously, if they went into
7 renal failure, then it's a different issue.

8 DR. FIRESTEIN: Yes. I agree with your
9 assessment of the severity of those side effects. But
10 there is again this issue of informative censoring,
11 ff people are dropping out -- and, in fact, you can
12 predict people that are dropping out based on that --
13 then it makes the analysis extremely difficult.

14 DR. WILLIAMS: That's why I think you need
15 both analyses, because I think the completing patient
16 is helpful clinically, but if all of those patients
17 dropped out because of severe -- they died -- you
18 know, we don't have much data on them. Then I think
19 you would want to know that.

20 So then you have to include that in your
21 intention to treat, because you don't know why those
22 people dropped out. It may have been for acne and
23 hirsutism, but it could have been for a lot more
24 serious thing.

25 DR. PETRI: Dr. Harris, may we please

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1 respond to some of those comments?

2 ACTING CHAIRMAN HARRIS: Dr. Petri, I am
3 going to allow you to respond.

4 DR. PETRI: Well, these are points of
5 clarification. So first we would like to give you the
6 mean time on treatment. Dr. Gurwith.

7 DR. GURWITH: Mean time on treatment was
8 361 days. So most of the patients -- the dropouts are
9 continuous throughout the year. Obviously, more than
10 half the patients achieved approximately a year. The
11 second is just remember that in the intent to treat
12 population which we showed you, SLEDAI >2 with the
13 window, the P value is .017.

14 So in the target population, at least in
15 the sponsor's analysis plan, we do achieve statistical
16 significance in the intent to treat population, even
17 though all the dropouts in that population are
18 considered nonresponders.

19 ACTING CHAIRMAN HARRIS: Okay. Let's move
20 to question Number 3: Please discuss the study 95-02
21 efficacy findings, including the results of the
22 originally specified primary analysis plan, as well as
23 the findings obtained using the amended analytic
24 plans, using the 60-day window, the SLEDAI>2 analyses,
25 and the change in responder definition. Please

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1 discuss from statistical and clinical viewpoints the
2 amendments to the original analytic plan.

3 It seems that we are following something
4 here. Let's start with our statisticians, so we can
5 get you out of the way. We know what you are going to
6 say.

7 DR. ELASHOFF: Thanks a lot. It seems to
8 me we already discussed deciding that people had to be
9 followed for 60 days -- on treatment for 60 days, and
10 we already discussed the SLEDAI >2. But now the issue
11 has to do with do you consider as a responder somebody
12 whose scores on one or more of the measuring
13 instruments actually went down rather than staying
14 exactly the same or going up?

15 While I feel that it is reasonable to
16 define some mutually agreed on window around zero so
17 that you don't necessarily exclude people who might
18 have gone down just a tiny little amount, I think the
19 results ought to be more robust to the exact choice of
20 what that is, and from the looks of it, right around -
21 - closely around zero, you don't have significant
22 results at all. You have to go fairly far down in
23 terms of getting -- in order to get a significant
24 result.

25 Therefore, I am unhappy with the

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1 apparently arbitrary choices which are not consistent
2 with what you get when you look at it with zero.
3 Later on, I am going to say that I think there would
4 be far better ways of trying to deal with multiple
5 scales than defining it this way at all.

6 ACTING CHAIRMAN HARRIS: Before we go on:

7 So if one were to ask what is your level of
8 satisfaction with the conclusions drawn, given these
9 modifications made later on, as a statistician are you
10 comfortable enough?

11 DR. ELASHOFF: No. I would not -- If the
12 results -- If finding a significant result is based on
13 making all three of these after-the-fact
14 modifications, none of which I agree with, then I
15 would not believe in those results.

16 ACTING CHAIRMAN HARRIS: Is that the
17 unanimous opinion among the --

18 DR. ANDERSON: I would like to say
19 something about the window. I don't have any
20 objection to the window in principle, and it does seem
21 odd that it wasn't decided upon earlier, given that it
22 was based on -- It was based on baseline data, which
23 would have been available, you know, a good deal
24 earlier, I think, than the trial finished. But the
25 idea of using the reliability of, you know, the

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1 standard deviation -- you know, the repeat measure
2 standard deviation, basically, is to give you your
3 cutoff is quite a reasonable one.

4 So since the cutoffs chosen were pretty
5 much consistent with that, not absolutely but very
6 close to that, I don't have any problem with that in
7 principle. Just the timing of it seemed a little
8 strange. So that's all.

9 DR. STRAND: Could I clarify?

10 ACTING CHAIRMAN HARRIS: Yes. Can I have
11 Dr. Tilley comment? In fact, I tell you what I'll do,
12 Dr. Strand. Let me just get some more comments around
13 the table so that we can -- and give an opportunity,
14 and I will give an opportunity for a response.

15 DR. STRAND: Thank you.

16 DR. TILLEY: Well, two things. One is, as
17 I mentioned earlier, I am comfortable with the
18 SLEDAI>2 categorization in that analysis, because of
19 the fact that they did the exploratory and then this
20 was confirmatory. So I was very comfortable with
21 that.

22 I have similar concerns about the window
23 and about the approach to analysis. Let me just point
24 out, too, that it seems to me that what they are
25 actually doing with this window is trying to define

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1 someone who stays the same. Really, they are not
2 defining improvement with that window. I think that
3 is just something to think about.

4 ACTING CHAIRMAN HARRIS: Let me turn to
5 the sort of right side of the table. Maybe, Dr.
6 Liang, you would like to comment.

7 DR. LIANG: Which? I think we have
8 discussed this. Which one of these things?

9 ACTING CHAIRMAN HARRIS: Well, the window.

10 DR. LIANG: It took me a while to figure
11 out what the window was.

12 ACTING CHAIRMAN HARRIS: It isn't only the
13 window, but the whole principle later on of modifying
14 the study in the particular way they did, and then,
15 you know, arriving at the result and how valid is this
16 result?

17 DR. LIANG: You know, I've been involved
18 with, I thin, seven DSF sort of lupus studies, and
19 those committees are just getting a workout, because
20 we are learning things as trials emerge. One of them
21 is to try to change things, but still honor the
22 principles of good science.

23 So I asked myself, were any of these
24 findings based on, you know, polling the data and
25 looking to emphasize an effect. At least from the way

1 it is presented, I can understand it. It seemed a
2 fair way to do it.

3 Every time they did it, they were blinded
4 to the data, and they thought of things that we should
5 have thought of out in the beginning, like the concept
6 that these instruments have variation and that perhaps
7 that is a normal undulation around a baseline. That
8 is something we had not done, because we had never
9 measured these activity measures in 300 patients.

10 So I think that all of the decisions are
11 justifiable and, from what I hear, the process by
12 which they were done were done in a scientific way.
13 I mean, realizing that we don't have any tabula rosa
14 about how to do these things.

15 So I was comfortable with hearing the
16 process and the objectivity that I heard.

17 ACTING CHAIRMAN HARRIS: Dr. Silverman.

18 DR. SILVERMAN: I think, certainly, the
19 SLEDAI of 2 was very reasonable. I would have to
20 agree with almost everything that was said.

21 My only concern is a specific window
22 around the VAS. I know I have sat at other meetings
23 where I have never heard of a VAS varying by 10
24 millimeters from patient to patient -- on a patient or
25 a physician global assessment varying by 10

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1 millimeters. In fact, I've heard it's far more
2 accurate.

3 So I was very surprised at that. I can
4 understand from day to day variation, but why haven't
5 we ever had a window then in other studies? My
6 question -- and I've seen RA studies where I choose
7 VAS as physician global, and I have never seen a
8 window go in. So how was that picked now?

9 DR. ANDERSON: Yes. We're using the term
10 window now, and I also was when I was talking earlier,
11 talking about the variation rather than the 60-day
12 window.

13 DR. SILVERMAN: No, no. I agree with you.
14 I'm talking about that, if you get a VAS of 30 and a
15 VAS of 39, that that is considered the same, if I
16 understand what we are talking about.

17 DR. ANDERSON: Well, the within-person
18 variation in many VASes is something like 30.

19 DR. SILVERMAN: Okay.

20 DR. ANDERSON: They have much larger --

21 DR. SILVERMAN: So why do we use them, and
22 why don't we use it -- No. Then I will question
23 using that as a scale, period. Why do we even bother?

24 DR. ANDERSON: They are unreliable, but
25 they are sensitive to change.

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1 DR. SILVERMAN: But we've never used it.
2 I think the last final question: Why has a window
3 never come up in an RA study?

4 DR. ANDERSON: Well, can I respond to
5 that? Well, you know, the ACR 20 requires 20 percent
6 improvement in various measures, and that gives you a
7 bit of a window.

8 DR. SILVERMAN: No, it doesn't. That's 20
9 percent plus another ten. No, it's not a window.
10 It's not a window. It's a change. It's not a window.

11 DR. ANDERSON: Yes, true. True.

12 DR. WILLIAMS: In the CSSRD studies, we
13 didn't use a Leicher scale rather than a VAS, but we
14 gave one point either way as considering no change --
15 as being considered as no change.

16 ACTING CHAIRMAN HARRIS: I'll give Dr.
17 Strand a chance, and then we will keep going.

18 DR. STRAND: I wanted to just clarify a
19 few things. When we had our first meeting with the
20 agency about the whole program, we at that point
21 discussed -- and this was in '95 -- this protocol. We
22 had the design and so on, and we talked about that no
23 worsening could be considered stabilization, could be
24 considered as good as improvement. But we did talk at
25 the time that there was variability in the

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1 instruments, and there would be variability around
2 what would be considered to be worsening.

3 It was agreed that the sponsor would come
4 back with a definition for those sort of variabilities
5 at a later time point, but that they could start the
6 study.

7 Now the SLEDAI>2 is an evidence based
8 amendment that came after 94-01 was analyzed. The
9 window actually preceded that idea. If you take that
10 away from the other discussion, it was really
11 something that the sponsor needed to do some more work
12 on to figure out what the definitions were.

13 I was not at the time involved in the
14 program when those definitions were submitted for the
15 final analysis plan, but I did even ask two weeks ago
16 if they would look at the pre-treatment screening and
17 baseline values for all of these parameters and see
18 how they corresponded to the windows. Lo and behold,
19 they are almost identical, as you saw.

20 So this was well after unblinding, looking
21 at pre-treatment data. In fact, you know, the ACR 20
22 is five out of seven criteria, and it requires a 20
23 percent improvement to actually -- a 20 percent change
24 to actually show improvement, indicating that
25 variability of disease course, underlying disease

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1 course can be accounted for in the less than 20
2 percent improvement.

3 That was the idea behind this window
4 definition as well.

5 DR. FIRESTEIN: I think that the notion of
6 the window -- Now we have evolved from the 60-day
7 window to a different window here. But the idea of
8 the window is actually quite brilliant and is also
9 clinically intuitive.

10 My comments really have to do with
11 intuition, not statistics, and I apologize for those
12 of you who have much greater expertise in this area
13 than I do. But if you have a window that, for
14 instance, in the VAS of, say, 10 millimeters or so,
15 wouldn't you also expect -- wouldn't you also require
16 some sort of similar level of improvement to have
17 clinical meaning?

18 So, for instance, the VAS -- Again, we
19 have stated that it is essentially ten millimeters of
20 difference either way. If at the end of the study we
21 find that for the group the change is five
22 millimeters, although I understand that that's for the
23 group and not for an individual patient, what is the
24 clinical meaning of an improvement that falls within
25 the experimental error of your assay?

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1 That is essentially what the ACR 20
2 attempts to solve, and that is you give people wiggle
3 room that there's going to be some people who get a
4 little better, some people who get worse, and then you
5 set your window for what you are calling better to be
6 bigger than what's beyond placebo effect, experimental
7 error, intra-observer variation.

8 It seems to me that, if we are going to
9 use windows in order to allow people to get a little
10 bit worse without calling them worse, we have to use
11 the same window on the other side in order to call
12 them really -- to say that they have really gotten
13 better. I think maybe the statisticians can comment
14 on that and help me.

15 DR. ANDERSON: I would just like to say
16 that in this trial what is called improvement is a
17 misnomer. It's really not worsening. There isn't
18 really a definition of improvement using these windows
19 in this trial, I would say.

20 DR. PETRI: Dr. Harris, may I clarify? I
21 agree entirely with you, Dr. Anderson. The point here
22 was stabilization or improvement. That's why we are
23 looking at the window in this fashion. We are not
24 trying to define improvement. We are trying to define
25 not worsening.

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1 Dr. Elashoff, I wanted to respond to your
2 comment as well. You were concerned that, if we
3 averaged the window for the different instruments,
4 it's about ten percent. But in fact, if you wanted to
5 pick a more stringent window, this study meets
6 statistical significance for three percent, if you
7 chose that as the window.

8 DR. ELASHOFF: But not if you choose zero.

9 DR. PETRI: No, but that was the whole
10 point. That was the whole point of this discussion.

11 DR. JOHNSON: Well, it's debatable whether
12 or not the data will rise or fall on this alone, but
13 you know, it's not as if we were unaware of the
14 variability measures when we designed this trial. We
15 even thought about the words that we are using. You
16 can read it in the protocol, and it is improvement or
17 stabilization, like Michelle said.

18 There was explicit discussion about what
19 that cutoff should be. You know, it was just made at
20 a particular point and not the point plus ten percent
21 or the point minus ten percent at the time of the
22 protocol design.

23 DR. WILLIAMS: But there's enough patient
24 variability that I think that it's very reasonable to
25 have a plus or minus, and what you decide on that is,

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1 you can make those decisions. But as we have already
2 talked about, ten percent is not unrealistic. If you
3 gave the same test the next day, they may be
4 different, and some of them would be lower.

5 DR. JOHNSON: Yes. I'm sure there's an a
6 priori argument for incorporating variability, and
7 some of these measurements have huge variability. We
8 don't have Dr. Lassere here to give us that data, but
9 it's true. Across a lot of these measures, especially
10 the VAS measures, there's big variability.

11 DR. CALLAHAN: I just wanted to agree.
12 I'm very comfortable with having some window, because
13 these measures have a huge variability, and it sounds
14 like there was some discussion initially. Dr. Strand
15 said that you would come back with the assessment. It
16 just wasn't put in, or written explicitly.

17 ACTING CHAIRMAN HARRIS: Dr. Sherrer.

18 DR. SHERRER: I guess my comment on
19 looking at all of this is that there are deficiencies
20 scientifically, if you want to be pure. I guess as a
21 clinician, I'm thinking about this drug and what it
22 might do for our patients who are using it anyway.
23 And I'm going to go off a little bit here and say that
24 they've shown the drug to be reasonably safe, I think
25 quite safe.

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1 This is a drug that our patients are using
2 anyway, and if the data is even suggestive, though the
3 statistics are imperfect, then I think I would like to
4 have a drug like this available so that my patients
5 don't have to use it from sources that are not
6 necessarily standard in what's in this.

7 ACTING CHAIRMAN HARRIS: I am going to go
8 around the table this time, and I am going to ask
9 something -- I'll ask your comfort level in terms of
10 the use of these amendments to demonstrate efficacy of
11 the drug, given the definitions that we were using as
12 efficacy.

13 So how comfortable are you that -- We
14 understand that it isn't pure, but how comfortable are
15 you as to whether or not, with these amendments, that
16 at least the results have some meaning?

17 DR. TILLEY: I think I'm comfortable with
18 parts and not comfortable with others. I still have
19 a question mark in my mind about the efficacy or the
20 effectiveness of this drug.

21 I like the idea of the window, but what I
22 don't like is that what I read here is that the final
23 version of the analysis plan was received April 30,
24 1999, which is almost a month after the last patient
25 completed their treatment in the second trial. So I

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1 just feel very uncomfortable with that.

2 DR. ELASHOFF: I think the issue is what
3 is one's standard of proof that efficacy has been
4 demonstrated. When you have to make several
5 modifications in issues of intent to treat and looking
6 at subgroups and changing definitions, then I'm very
7 uncomfortable with using those results.

8 In addition, if one looks at it in terms
9 of not worsening, we are only getting about 50 percent
10 of people not worsening, and that means that at least
11 50 percent are worsening. Even at best, the
12 differences that one might guess between the results
13 are only in the order of ten or 15 percent.

14 So I'm very uncomfortable at making all
15 these modifications and saying, well, as long as it
16 comes out significant for something, we'll count that.
17 I'm quite uncomfortable with that.

18 DR. ANDERSON: I don't like the 60-day
19 business at all, and with the SLEDAI>2 I don't like
20 that in the first trial, but it's okay in the second,
21 I think, because it was based on the experience in the
22 first.

23 Then with the variability of the measures,
24 I feel comfortable with that one, too. So basically,
25 the main thing that I have a problem with is the 60-

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1 day window in the second trial and SLEDAI>2
2 restriction in the first trial.

3 DR. BRANDT: On a 100 millimeter VAS
4 scale, I'm about a 60.

5 DR. CALLAHAN: I'm comfortable with the
6 way Dr. Tilley had put it about the greater than 2
7 SLEDAI, thinking of the first study as exploratory and
8 the second study more confirmatory.

9 I'm comfortable with the parameters set
10 around the VAS scale and the changes. And as a non-
11 clinician, I must say, I am swayed by the arguments
12 from the clinicians of the value of having the 60-day
13 looked at, in addition to the intention to treat, but
14 I think the intention to treat should be first.

15 ACTING CHAIRMAN HARRIS: Okay. I would
16 say that I am comfortable with the greater than 2, and
17 perhaps I'm comfortable with, in fact, setting that
18 window such as it is.

19 What I am a little uncertain about is just
20 the number of amendments that had to be introduced,
21 because -- and this is really -- I know I am having
22 some personal difficulty, because we have set
23 standards that we are not even sure about when we
24 start out, and I think it isn't unexpected that as we
25 go along the way that we are going to have to modify

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1 whatever that line in the sand is.

2 I think if, however, there are too many
3 changes, you have to make amendments in terms of
4 setting that line, then there's a degree of
5 discomfort. Subjectively, I feel as if -- You know,
6 subjectively, I feel that there is something of value
7 that has come out here, but scientifically, and I
8 think, ultimately, with respect to the FDA, with
9 respect to the responsibility to the public, I think
10 there are certain rules that, more or less, we should
11 follow.

12 So for that reason, I would say I am a
13 little uncomfortable about the number of amendments
14 that had to be made to show efficacy here. If it were
15 one or two, but you know, there just seem to be a few
16 more than one or two.

17 DR. FIRESTEIN: Can you clarify what I'm
18 supposed to be comfortable about?

19 ACTING CHAIRMAN HARRIS: Do you think,
20 given the amendments that were made, that these
21 results are meaningful enough to say that this drug
22 has demonstrated efficacy?

23 DR. FIRESTEIN: Safety and efficacy?

24 ACTING CHAIRMAN HARRIS: Safety and
25 efficacy. Yes. I changed the question. Okay. Does

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1 anybody want to change their answers? Okay.

2 DR. FIRESTEIN: Okay. As with our
3 statistical or statistician colleagues, I have a
4 certain degree of discomfort with the 60-day window
5 and also with the plethora of amendments. On the
6 other hand, all things in toto suggest that there
7 might be some marginal or modest benefit, and I think
8 that is certainly something that is important in an
9 area where there had not been any new drugs approved
10 for a long time.

11 A couple of other points, though: One is
12 I think that the safety issue is still open. When we
13 talk about safety and the ability of this as a steroid
14 sparing agent to be safer than using prednisone, there
15 we don't talk about a seven or nine-month trials. We
16 talk about what happens over five years or ten years.

17 Let's say we had the studies the other way
18 around, that we used prednisone as a DHEA sparing
19 agent. We would say that at seven or nine months with
20 7.5 milligrams of prednisone that it would be very
21 safe and very effective, but it's only after three or
22 five years that we would start seeing problems.

23 So I think our interpretations in terms of
24 safety over low dose prednisone still has to be held
25 in abeyance. I mean, I just don't think we know.

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1 I think that there probably is a marginal
2 benefit that's been shown. I think one does need to
3 be careful about offering the imprimatur of a panel of
4 experts or the FDA on something where the safety
5 issues are still open and the efficacy issues are
6 still debatable, although probably for many of the
7 reasons discussed, fall to the side of positive
8 efficacy.

9 I don't think the fact that our patients -
10 - speaking as a clinician, that our patients go to the
11 pharmacy and buy their drugs already there, buy DHEA
12 over-the-counter, is a reason to simply provide that
13 imprimatur. I think it cuts both ways.

14 I think, if it doesn't meet the standard
15 that we would hold for all other drugs that would pass
16 through this process, even whether they are available
17 or not, then we would be doing them a disservice.

18 ACTING CHAIRMAN HARRIS: Thank you. The
19 safety issue is question number 5. So if you remember
20 my original question, let's keep going. Dr. Sherrer?

21 DR. SHERRER: Thank you. As it relates to
22 the cutoff of the SLEDAIs, I'm very comfortable with
23 that. I think that makes good clinical sense.

24 I agree that the number of modifications
25 makes one feel uncomfortable, but I think they all

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1 have good rationale behind them, and they were done
2 while the study was still blinded. So I think it
3 doesn't change the data, and using things that are
4 rationale, while not purely scientific - I'm not a
5 statistician, certainly, but I think clinically they
6 make sense.

7 So I wouldn't want to discount that just
8 because it was not perfect science, because it can be
9 supported by clinical rationale thinking, and I think
10 it's meaningful, and I think it makes a difference to
11 me.

12 I look at this and would think, well, this
13 isn't a great drug. It is a drug that has some
14 benefit and seems to be safe.

15 DR. WILLIAMS: In answer to your first
16 question, I am comfortable with the SLEDAI>2, and I'm
17 comfortable with the variability around the
18 instrument. I am not comfortable with the 60-day. I
19 would rather have them report on those who persisted
20 on the medication throughout the trial rather than a
21 group that just took a window of drug.

22 In answer to the second one, I think that,
23 while the data is not perfect, I think that it does
24 show some modest benefit, and I would rather see it
25 managed by control rather than by health food stores.

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1 MS. McBRAIR: I agree with the SLEDAI > 2.
2 I think that that's a good to look. It's measurable,
3 and it sounds like it's new and exciting work in the
4 area of lupus.

5 I think the people need something new.
6 The patients need something new. The physicians need
7 something new. And it might be part of the arsenal
8 that they will be able to look at and use.

9 So I encourage additional studies related
10 to safety, but we'll never get them if people are
11 getting it at the health food store instead of through
12 physicians and through studies with companies. So I
13 would encourage that we continue to move on, but that
14 it's looking good.

15 DR. SILVERMAN: Well, the SLEDAI is easy.
16 You've heard my comments on VAS. Overall, I would
17 have to say that, speaking to biostatisticians, it's
18 not an efficacious drug, because it didn't meet the
19 criteria, but it is probably effective in patients who
20 take it for at least 90 days who have a SLEDAI over 2,
21 because that's what the data shows, using this
22 efficacy versus effective argument.

23 I do have one question, because it was
24 brought up. If this drug is approved for the use of
25 lupus, does that mean you can't get it in health food

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1 stores anymore? That's an assumption this panel is
2 making, and that's biasing some people's comments.

3 So I just want to hear from the FDA. Is
4 that what is going to happen, because people are
5 saying, if we approve it, you can't buy it in your
6 health food store. So that's a reason to approve it.
7 I want to be assured that that is going to happen, if
8 that is going to influence anybody's decision.

9 DR. BULL: I don't think I can really give
10 you a definitive answer to that. It's more of a
11 legal question, and the DSHEA, the Dietary Supplement
12 Health Education Act -- there are a number of other
13 legal mandates that will play into this. So I'm sure
14 we can't give you a definitive answer on that, and
15 whatever solution there is will be rather complex.

16 DR. SILVERMAN: I knew that was the
17 answer, but I just wanted -- I wanted to get it on the
18 table, because I've heard comments that say, if we
19 approve it, people aren't going to take it from their
20 health food store, and I would say, in fact, they
21 might take it more, because it might very well be
22 cheaper.

23 There is a flip to this argument that
24 people who are putting forth that argument must
25 consider.

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1 DR. FIRESTEIN: Well, not only would it be
2 cheaper, but it would have the official stamp of
3 approval for a disease indication, and I think that we
4 shouldn't be recommending approval because our
5 patients are already getting the drug someplace else.
6 We don't do that for drugs in San Diego. People go to
7 Tijuana to pick up things that are completely
8 uncontrolled. So I think that that would be a
9 spurious argument.

10 DR. LIANG: I've spent a lot of time
11 looking at dirty data with a clean mind. So I can
12 live with all those decisions.

13 ACTING CHAIRMAN HARRIS: Dr. Klippel.

14 DR. KLIPPEL: I thought he was going to
15 have the rest of the comment there.

16 To me, given how little we know about the
17 clinical trial methodology of lupus, I, quite frankly,
18 would have been surprised if this would have worked
19 without some modifications. I think that in many ways
20 this has been an experiment in uncharted waters.

21 I think all of these modifications have
22 been learning experiences and, from what I've heard,
23 a lot of thought has gone into them, and I think that
24 they are going to be very instructive for anybody else
25 who begins to design trials for drugs.

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1 So I, quite frankly, think this has been
2 a positive experience, and I'm perfectly comfortable
3 with all these amendments.

4 ACTING CHAIRMAN HARRIS: Thank yo. Ms.
5 Fields is a patient.

6 MS. FIELDS: She does have a voice. Since
7 new drugs come out for lupus once every 40 years, I
8 figure this might be the only chance I have to talk.

9 The one comment I wanted to make is --
10 This is a question. Are not the FDA folks involved in
11 making the amendments, the adjustments when they come
12 up with a new design protocol? Is the FDA involved in
13 the new design protocol after the first trial?

14 DR. JOHNSON: Well, everything is
15 submitted to us. What do you mean, involved, though?

16 MS. FIELDS: Are you involved in the
17 discussion?

18 DR. JOHNSON: Sure, but we, as I mentioned
19 before, as a matter of scientific principle, had said
20 all along that these analyses can be secondary
21 analyses.

22 MS. FIELDS: Okay. So basically, am I
23 understanding that the discussion we are having today
24 has taken place before in the sense of you were
25 involved -- Was this committee involved in making that

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1 design at all? So it was just FDA? If they wanted to
2 make changes in their protocol, did it have to be
3 approved by the FDA?

4 DR. BULL: I think there's a difference
5 conceptually in terms of -- You are asking was it
6 approved by us? Was it discussed? Yes. In terms of,
7 in a sense, a hierarchy of how it would be viewed,
8 there is a difference of opinion in terms of the
9 appropriate way that this data should be viewed.

10 I think it's the totality of the evidence
11 as to whether or not you look at this as a secondary
12 analysis, whether or not the data is so compelling
13 that it overrides the originally defined one that
14 failed. I think it is really looking at the total
15 picture, and I think we all have to appreciate that
16 there are many layers to looking at the clinical
17 issues, the scientific issues, the design issues, the
18 methodological issues.

19 I think someone cited the uncharted waters
20 in study design for lupus. So all these things have
21 to come into play. But I guess for your question as
22 to whether or not we approved it, I think you are
23 asking did we say yes, it's okay. And it's not quite
24 that simple.

25 MS. FIELDS: Okay. My thought was, if you

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1 had, it was sort of redundant to be discussing it
2 again or we made the mistakes originally and now we
3 are living with them, if you felt they were mistakes.

4 Since I may not get to talk again, may I
5 make one other comment? I have lived with lupus for
6 12 years. There is no good treatment for lupus.

7 If you count prednisone, it saved my life
8 on several occasions, but it certainly is not a good
9 medication when you talk about side effects, and I do
10 take Danacrine which causes the same side effects that
11 DHEA do, and they are livable.

12 I know the patient came forth with -- the
13 female that said that living with acne and with -- and
14 I can't even pronounce that other one -- hair -- I had
15 asked him what it meant: What's that? Oh, I have
16 that. But those are livable side effects.

17 If DHEA can provide for the lupus patient
18 relief -- and I know several of my friends who do get
19 it through the Internet, and I'm not saying that
20 that's good and that's proper, but they do work with
21 their doctors, and for the first time in their lives
22 they have had relief.

23 They have continuous lupus flares. Some
24 patients do have that. I don't have that, but some
25 do. I think, with the continuous flare, that that

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1 type of person looks for something, and they are going
2 to look anywhere. Not that that's a reason to approve
3 it, but I was kind of wondering what kind of clinical
4 responses the doctors have seen in their own practice
5 and that, hopefully, they do come and tell you when
6 they are taking DHEA, because it could be very serious
7 if they weren't.

8 People are concerned about things like --
9 It now comes in 25 milligrams over-the-counter, and
10 it's going to go up to 200, I hope, I guess, if it
11 gets approved. So you wouldn't have to have so many
12 pills to take. But the question then becomes, you
13 know, will it be approved? If it's approved, would
14 your doctor then be willing to prescribe it? Would
15 your insurance be willing to pay for it?

16 So they have lots of concerns that they
17 have asked me to share with you, and I just wanted to
18 bring that to you.

19 The one person I was telling you about
20 that I just talked to before I left that's been
21 continuously plagued with lupus flares forever, she's
22 a psychiatrist, and she is now down to five milligrams
23 of prednisone. She's never been able to get below 20,
24 and this is the first time she's had quality of life
25 enough to enjoy herself. For the last 12 years, she's

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1 had lupus.

2 So a lot of times you can get bogged down
3 in statistics and design, and I know those are
4 extremely important. But those of us out in the field
5 who have the disease are really excited that there's
6 something in the pipeline that might be helpful,
7 useful, give us quality of life. So please consider
8 us when you consider the design flaws. Thank you.

9 ACTING CHAIRMAN HARRIS: Thank you very
10 much, Ms. Fields. We are entirely advisory, but we
11 must make judgments based on data, efficacy, and we
12 have to -- We are charged with protecting the public,
13 too, in terms of safety.

14 Hopefully, this has been helpful. I don't
15 know that you were able to go away with any clear
16 decision here, but I think the discussion has been
17 helpful.

18 We will take a break. There are two more
19 questions to go. I thought that we could break for
20 ten minutes and then resume, and then complete the
21 questions before us. Thanks.

22 (Whereupon, the foregoing matter went off
23 the record at 3:16 p.m. and went back on the record at
24 3:29 p.m.)

25 ACTING CHAIRMAN HARRIS: I would like to

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1 resume.

2 DR. PETRI: Nigel, is it possible for me
3 to make the comment now?

4 ACTING CHAIRMAN HARRIS: I am giving Dr.
5 Michelle Petri a chance to make a comment. Dr. Petri.

6 DR. PETRI: I think the committee has
7 already voted, and I know there wasn't a unanimous
8 decision, but many of the committee members felt that
9 the SLEDAI>2 and a measurement tolerance were
10 acceptable.

11 If you do accept those two principles, a
12 SLEDAI>2 and measurement tolerance for stabilization,
13 then all of the analyses of 95-02 are statistically
14 significant. That means the intent to treat,
15 obviously, with a P value of .017.

16 ACTING CHAIRMAN HARRIS: Thank you. I
17 don't know, Dr. Johnson, would you like to make a
18 comment or you'll just let that ride?

19 DR. JOHNSON: Well, you know, there's a
20 lot of themes going on here, and one is -- I think in
21 the end, the question is do all these -- I think it's
22 mistaken to think that all these analyses sort of
23 coming out of the gate have equal evidentiary weight.
24 I mean, they just don't, when you use the null
25 hypothesis model.

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1 It's not to say that there can't be, you
2 know, sometime in certain scenarios situations where
3 you are so taken on a clinical basis that you let your
4 clinical persuasion essentially trump the statistics
5 or trump the logic that goes into making a decision as
6 to pro or con from the result of a trial.

7 It is also true, I think, that again from
8 an inferential point of view any decision to change a
9 protocol once data has been seen, whether it's blinded
10 and pooled and everything else, that is information,
11 and that may introduce a bias, and you can't
12 quantitate that bias, I think. Those are just the
13 scientific dimensions of these things.

14 ACTING CHAIRMAN HARRIS: Thank you. We
15 are going to push on.

16 Question Number 4: Please comment on the
17 differences between placebo and DHEA in study GL95-02
18 in discontinuations for any cause and discontinuation
19 due to adverse events. Do higher withdrawal rates in
20 the DHEA treated group impact interpretation of
21 efficacy signals as per the sponsor's subpopulation?

22 Dr. Williams, would you like to start?

23 DR. WILLIAMS: I'm not sure I understand
24 the second half. But I think that, if any drug has
25 activity, it would probably have more withdrawals for

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1 adverse effects than placebo. So I was not surprised
2 that the drug had more withdrawals.

3 I'm not sure I understand the second part
4 of what does it mean in terms of the efficacy. I
5 think there are two separate issues.

6 ACTING CHAIRMAN HARRIS: I'll ask the
7 second part of the question. I'll perhaps turn to our
8 statisticians and ask that. But let's look at the
9 first part of the question some more, if we could
10 examine. Please comment on the differences between
11 placebo and DHEA in 95-02 in discontinuations for any
12 cause and discontinuation due to adverse events.

13 Perhaps, Dr. Firestein, would you like to
14 comment about that?

15 DR. FIRESTEIN: No. Well, yes, I suppose
16 I could. I mean, i think it raises some of the
17 problems with the 60-day window again, but the adverse
18 events seem to be relatively minor. And as was just
19 stated, with an active agent it is not unanticipated
20 that there would be a certain number of AEs and SAEs.

21 DR. ELASHOFF: I'll just say that any
22 imbalance in dropout rates make it more difficult to
23 assess what is going on with efficacy, because there
24 is potential for bias of one sort or another.

25 I mean, for example, one could argue that

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1 the ones in inactive treatment group who drop out due
2 to adverse events wouldn't have dropped out if it had
3 been effective and they have the adverse events. So
4 that's just a sort of worst case kind of scenario that
5 makes one worry more about interpreting efficacy
6 results when there is imbalance in dropout.

7 ACTING CHAIRMAN HARRIS: Dr. Elashoff,
8 maybe in the second part of the question, do you
9 think, though, that because of these dropouts that
10 perhaps there is a fatal flaw in terms of
11 interpretation of efficacy?

12 DR. ELASHOFF If results, no matter which
13 outcome variable you looked at, no matter which
14 population you looked at, were very consistent, then
15 one is less worried about any particular problem. But
16 when there tends to be inconsistency in results -- and
17 I'm not talking about just little differences in the
18 P value, going from .04 to .07 or something, but real
19 inconsistencies in the results from one analysis to
20 another, one subgroup to another, one outcome variable
21 to another -- then the addition of other problems like
22 this just deepen the concern.

23 DR. WILLIAMS: If you look at the
24 withdrawals for efficacy and for other, they were
25 essentially the same. So you are looking that there

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1 were 31 withdrawals from DHEA and 18 from the placebo,
2 based on adverse effects. It doesn't seem to be
3 unusual to me.

4 DR. ELASHOFF: I didn't subtract quickly,
5 but maybe that was a difference of 13 people. The
6 difference in the efficacy table with the same subset,
7 SLEDAI>2, treatment greater than two months using
8 modified window is 87 responders on GL701 and 65 on
9 placebo. That's a difference of 23.

10 So we are saying 13 isn't -- a difference
11 of 13 isn't very much in one space, and 23 is big
12 enough to approve a drug in another.

13 DR. WILLIAMS: Usually, you would balance
14 out in that you have more lack of efficacy for your
15 placebo group and more toxicity in your active drug
16 group. We didn't see that on this one, but there are
17 no alternatives to therapy either.

18 ACTING CHAIRMAN HARRIS: Let me press some
19 more. Dr. Liang, perhaps again I'll ask a comment.

20 DR. LIANG: I have the same -- That's why
21 we use the ITT standard for efficacy. But what you
22 see is not unusual, I don't think.

23 ACTING CHAIRMAN HARRIS: Are you
24 comfortable that you've gotten what you wanted? Okay.

25 Then we'll go to question number 5:

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1 Please discuss the safety findings in both studies.
2 Please include comment on proteinuria, hematuria, and
3 complement levels.

4 In dealing with this question, I think we
5 need to deal with broad safety issues as well as this
6 hematuria. So I really don't want to limit the
7 discussion to hematuria, proteinuria and complement.

8 DR. WILLIAMS: Although I would say that
9 the biggest concern I had in reading the results of
10 this study where in 600 patients there were a few that
11 had significant renal disease -- now this is in a
12 population of patients who are going to have renal
13 disease, but I am concerned that there may be some
14 renal toxicity that's not been identified in a
15 relatively small number of patients.

16 ACTING CHAIRMAN HARRIS: One more. May I
17 just press a little more with Dr. Williams? What
18 would you recommend? I mean, it seems kind of
19 obvious, but the point is in terms of -- given that
20 uncertainty, if you will, you know, how might one --

21 DR. WILLIAMS: Well, the real problem is
22 you've got a disease that can do this by itself, and
23 they had explanations for a lot of the patients. But
24 there was enough change in protein, hematuria, a few
25 patients increased their creatinine and there were

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1 complements that I'm less concerned about, but
2 suggesting that there was an effect on the kidneys.

3 Now that may all be disease related, and
4 I don't think you can answer it in a clinical trial,
5 because I think this is going to take lots of patients
6 to determine, just as it will to determine whether
7 there's any malignant potential for a hormone therapy
8 like this, and it's got to be done through post-
9 marketing surveillance.

10 DR. SILVERMAN: My only comment is
11 regarding the proteinuria. I know that that was
12 dismissed as not as having no other renal signal, but
13 I would ask the nephrologists I know from the company.

14 Certainly, in renal lupus the first
15 signal, in fact, is only proteinuria. So I think the
16 fact that there were significant numbers of patients,
17 and there were more patients in the treated group who
18 had rising proteinuria. Acknowledged, there is no new
19 proteinuria difference.

20 I would wonder, knowing what this drug
21 does, whether in fact, if it were renal blood flow,
22 increasing filtration, wouldn't that then lead to, as
23 many people believe, that hyperfiltration or increased
24 filtration, in fact, is bad for the kidney, which is
25 the rationale behind the use of ACE inhibitors in

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1 diabetic nephropathy.

2 So are we seeing the reverse effect here?
3 I know some people have advocated ACE inhibitors for
4 membranous nephritis for exactly the same reason.

5 DR. MADAIO: Great point. It's a great
6 point, actually. It turns out that -- and I didn't
7 know this before I looked into it -- androgens don't
8 increase filtration fraction. So what happens is that
9 you increase renal plasma flow.

10 I'm Mike Madaio. Sorry. I'm a
11 nephrologist from University of Pennsylvania. What is
12 being referred to is the fact that hyperfiltration or
13 increase interglomerular pressure, in and of itself,
14 whatever the cause of disease, is deleterious.

15 So one of the concerns here is that,
16 because androgens increase glomerular filtration rate,
17 that that would be deleterious by causing
18 hyperfiltration and by causing an increase in
19 proteinuria.

20 Now it turns out that -- a couple of
21 things. One is androgens don't increase filtration
22 fraction in that they increase renal plasma flow, but
23 they don't cause glomerular hypertension. So the
24 proteinuria, while it still may be deleterious, as you
25 point out, there is not -- you wouldn't expect that

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1 there's intraglomerular hypertension in the patients
2 that don't flare.

3 So I'd be less concerned about that.
4 Whether or not low grade proteinuria is in itself
5 deleterious, we argue about all the time, and I think
6 that you are referring to that argument.

7 I think generally, if you look at cross-
8 sectional analysis of all patients, patients with less
9 than 2 grams of proteinuria do pretty well, no matter
10 what their disease is, from a renal point of view,
11 what their underlying disease is and how they are
12 treated.

13 So I would be less concerned about that
14 group, but in the patients who had the jump,
15 significant jump in proteinuria, and I define
16 significant jump as into the nephrotic range -- those
17 patients clearly had an increase in disease activity
18 in both groups. Did that answer your question?

19 DR. SILVERMAN: Almost completely, but
20 along the same point, with the new studies, again, one
21 has to go back to diabetic studies where calcium
22 channel blockers appear to work as good as ACE
23 inhibitors in altering the long term outcome, a
24 decrease in proteinuria.

25 Wouldn't that be more blood flow effect,

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1 more similar to maybe what we are seeing here, rather
2 than a pressure effect of an ACE inhibitor altering
3 the afferent pressures?

4 DR. MADAIIO: I'm not sure I agree that
5 calcium channel blockers work as well as ACE
6 inhibitors or ARBs, but certainly, lowering blood
7 pressure, which you see in both of those groups in the
8 anti-hypertensive therapies, is as important as
9 anything else, and we're quibbling about the
10 glomerular hemodynamics.

11 ACTING CHAIRMAN HARRIS: Thank you.

12 DR. ELASHOFF: I don't have any specific
13 comments on safety, but I do think that we ought to be
14 looking at confidence intervals for these rates from
15 these very small studies to remind us that, even
16 though the rate looks sort of small here, the results
17 are consistent with much higher rates than those that
18 have been observed, because of the variability due to
19 small samples.

20 ACTING CHAIRMAN HARRIS: Can I get then a
21 sense -- The sense I am getting from the committee,
22 because I think the issue is that, certainly, one is
23 dealing with an agent that at least so many of us
24 believe may have some effect in lupus, and providing
25 it is not terribly harmful, then one would say, you

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1 know, that we ourselves might be comfortable, despite
2 there not being all the scientific evidence we need,
3 that one might go ahead and use a drug like this.

4 I want to get a sense again whether or not
5 -- from the committee, whether or not -- I won't ask
6 you individually, but if there is anybody here who
7 would be terribly alarmed about some serious side
8 effect, some serious safety issue that might modify
9 what it is that we recommend.

10 I think, if there is a great concern about
11 safety, then we certainly would want to at least
12 modify some of what it is that we recommend.

13 DR. TILLEY; If I could just say, from a
14 statistical and epidemiologic perspective we don't
15 know the answer to that question.

16 ACTING CHAIRMAN HARRIS: That's right.
17 Yes.

18 DR. TILLEY: And Matt pointed out to me,
19 we rarely ever do know the answer to that question.
20 But I think the problem with this situation, if I
21 could just make some general comments, is that a lot
22 of the comments I'm hearing from the committee are
23 coming from the point of view that there is nothing to
24 offer patients beyond prednisone, and that here's
25 something that is potentially beneficial.

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1 It reminds me of some of the discussions
2 that I heard around the treatments for AIDS where
3 patients were saying there's nothing, there's nothing,
4 forget the clinical trials principles, give us the
5 drugs. We all know that that didn't work out very
6 well.

7 A lot of things got used that weren't
8 effective, and good things didn't get tested, and
9 patients were -- It just was a bad situation, and the
10 AIDS community has moved back to a more randomized
11 clinical trial model.

12 So what we are being asked to do here is
13 kind of skip those steps and say this is potentially
14 beneficial. What I'm concerned about is -- a couple
15 of things. First of all, the first trial ended in
16 April of 1997. So there was plenty of time to really
17 dredge those data, come up with protocol amendments
18 and ideas for this trial, the second trial, and yet
19 the protocol for analysis wasn't finalized until April
20 of 1999.

21 So I'm very concerned about this being
22 data driven, even -- I'm not saying unblinded, but it
23 just seems like it should have been data driven, but
24 it should have been data driven by trial one and not
25 by what they were seeing in trial two, unblinded or

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1 blinded -- blinded data, regardless.

2 The other thing is I think there is a
3 danger here that we are going to add to patients' --
4 we are going to give them false hopes, increased
5 costs, and an unknown potential of long term side
6 effects, and we are also not going to -- If we decided
7 against this, we're not going to keep them from
8 getting the drug, because it's out there.

9 So in a way, I feel like putting a
10 scientific imprint on this could be damaging, and
11 there's still a potential for them to get the drug, if
12 they want it. So I mean, it's not like we are keeping
13 something from them.

14 ACTING CHAIRMAN HARRIS: Can I ask for
15 further comment about -- I mean, that is some of what
16 we have been struggling with, quite frankly, all
17 afternoon. I think you capture it very nicely indeed.

18 DR. ELASHOFF: Apropos of that, at a
19 statistics meeting several years ago, an AIDS patient
20 got up and reprimanded the statisticians for allowing
21 people to do subgroup analyses and to encourage the
22 approval of drugs on subgroup analyses, which later
23 didn't pan out.

24 ACTING CHAIRMAN HARRIS: Thank you for
25 that comment. I turn to the clinicians, because we

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1 are on the front line, and the issue -- Again, we
2 often have to make decisions where the science -- and
3 there is the issue, or do we? But the question is,
4 you know, where one doesn't necessarily fulfill all
5 the sort of scientific rigor that is required, but at
6 the same time is there enough here to make one want to
7 give a blessing, if you will, to use of a drug that
8 there is something there is in terms of efficacy, and
9 we are comfortable.

10 We don't know what all the risks are, but
11 at this time the risks don't appear sufficiently
12 significant to prevent us using this drug. Now we are
13 talking about the safety issue, in particular.

14 Is there anything here that -- a signal
15 here at this time that would make us say, look, no,
16 this is not something that we would really want to use
17 or recommend its use?

18 DR. WILLIAMS: I think that I would use
19 it, but I would be hesitant in the patient with
20 nephrotic syndrome, because they had a couple who went
21 from two grams to 24, and that may have been the
22 disease. The other went from 2, I think, to 5. So I
23 may be reluctant to use it in nephrotic syndrome.

24 DR. BRANDT: Yes. It's not clear that
25 there are major safety issues. We have some dis-ease

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1 about the renal questions that have been raised, but
2 those are not going to be easily addressed. Another
3 clinical trial like this won't, I think, answer those.

4 Post-marketing surveillance and time will,
5 if there is anything there. So I see in the short run
6 nothing that's terribly disturbing or would want me to
7 proscribe the use of this on safety issues.

8 DR. SILVERMAN: This reminds me of many
9 drugs, certainly, I've seen in pediatrics come on and
10 what the agency has done, and I would recommend that
11 mandated post-marketing, not only surveillance but
12 actually true data collection in post-marketing.

13 That's been one of the ways the agency has
14 overcome small numbers in pediatrics, and it's been of
15 great benefit. What it had done -- and I see this as
16 similar to most of the diseases in pediatrics, because
17 of the small numbers, and that it's allowed us to use
18 drugs on a controlled condition, and we get the
19 answer, and maybe the answer may or may not be the
20 same one as today. But if there is this mandated
21 surveillance, one then has the answer.

22 If one has to change the recommendation,
23 you revisit it.

24 DR. ANDERSON: I don't know how to
25 interpret the pharmacologic studies. So I wonder if

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1 somebody could help with that. But there was -- Out
2 of 14 patients, there were three -- 14 normal -- These
3 are women without lupus. Three out of the 14 had some
4 blunting of ACTH stimulation response.

5 So that, despite the increased bone
6 density in some subjects, in subjects that were tested
7 for that, there could be long term, you know, bad
8 effects of this drug, like cortisol.

9 DR. SCHWARTZ: Mr. Chairman. I'm the
10 endocrinologist that designed that study. So I would
11 like to explain.

12 ACTING CHAIRMAN HARRIS: I was about to
13 ask for an endocrinologist.

14 DR. SCHWARTZ: Yes. I feel a little like
15 a duck out of water here with all these
16 rheumatologists, but maybe I can make endocrinology
17 easy for you.

18 Can we have the slide on, please? We need
19 the projector on. The slide is coming up.

20 We were very interested when we designed
21 this study to see if there was an effect of DHEA on
22 adrenal cortical function. Actually, maybe I could
23 show the steroid slide first, if you would pull it up
24 just quickly.

25 Just a little lesson in Endocrinology 101:

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1 The adrenal gland has three zones to it. The outer
2 zone are the mineralocorticoids that are necessary for
3 salt handling. The middle zone is the cortisol
4 pathway and these, of course -- prednisone is a
5 derivative of this, but these are, of course, your
6 anti-inflammatories.

7 Then you have this third zone here which
8 is the innermost zone. It's a little sliver in the
9 adrenal cortex which is the adrenal androgen pathways,
10 and where DHEA is.

11 When you give prednisone, you suppress all
12 three of these. Now we were interested to see whether
13 administration of DHEA would have an effect on these.
14 There is an interplay between these two. We know that
15 in chronic illness such as lupus and others as well,
16 DHEA levels are low, and there is a shunting more
17 toward these pathways.

18 So if we show the next slide then: As was
19 pointed out earlier, when we did the ACTH stimulation
20 test, it was done at baseline and at 28 days, and
21 these were normal, premenopausal women. They weren't
22 lupus patients, but pre-baseline you saw the mean was
23 about 230, well above the 200 mark that is usually the
24 normal response.

25 The important point here is that you went

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1 from normal to normal. So at one month they still
2 remained normal. What really brought this down was
3 these three subjects who were -- well, I don't know if
4 I want to call them outliers, but two of them had a
5 sluggish response even before they got DHEA, and it
6 was a little bit more sluggish at one month.

7 The third subject actually just made 200
8 nanograms per deciliter at this point. Now this is a
9 very modest and very small response. It's probably
10 not clinically meaningful.

11 Now I'll show you on the next slide what
12 I'm talking about. I mean, you are talking about a
13 ten percent reduction here in your peak response. The
14 next slide, please.

15 That's just a one-hour ACTH test. You can
16 look at the 24-hour urine-free cortisol which
17 integrates the entire response over a course of a day.
18 Unfortunately, when we made these, these bars are kind
19 of slivers, but what you see here on the 24-hour
20 cortisol, they are identical, either at Day One or
21 Day 28. So this is telling you that your overall
22 adrenal cortical function is normal.

23 So there are two points here, normal to
24 normal on the ACTH stimulation test. They still
25 remained in the normal range, and you are not

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1 affecting your overall 24-hour secretion.

2 Next slide, please. I wanted to show the
3 dexamethasone. Finally, just to put it in some
4 perspective, I showed you a trivial change in your
5 ACTH stimulation change. This is what you do if you
6 give dexamethasone for two and four days.

7 Actually, can you show the next slide?
8 This seems like it's squished up. Can we just pull
9 it up, please?

10 If you give dexamethasone for two days,
11 you get this sort of response. We're talking about
12 two milligrams dexamethasone. That's equivalent to
13 ten milligrams of prednisone. If you give it for four
14 days, you suppress your cortisol by 95 percent.

15 So I was showing you a trivial change in
16 ACTH stimulation in only one hour compared to what you
17 guys are doing with your prednisone.

18 Now keep in mind also that, even if you
19 are suppressing -- even if you do suppress your
20 cortisol responses by only ten percent, this is
21 trivial compared to what is going on with these
22 patients who are on steroids all the time anyway.

23 ACTING CHAIRMAN HARRIS: I think, without
24 a doubt, everybody would agree that we need to have --
25 if one were to go ahead and approve this drug, we

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1 definitely would need, of course, mandate post-
2 surveillance monitoring to be sure that are no
3 significant adverse effects with the agent. I think
4 everybody would agree that that is so. There just
5 isn't enough data here to say.

6 DR. FIRESTEIN: Yes. I think to summarize
7 what I've been hearing, the statisticians have been
8 saying that the data in many ways are flawed and can't
9 really make a clear decision based on classical
10 statistics whether there is true benefit, although
11 there are some subgroups where it could potentially
12 be.

13 The clinicians are saying maybe it works,
14 and I would say that, too, and that I would use it in
15 our patients without the statistical evidence to back
16 it up. The patients are saying do something, even if
17 you are not really sure it works.

18 I guess from my perspective, we need to
19 step back from all that and view it somewhat
20 dispassionately, which is what our charge is, and that
21 is determine -- as best we can, make recommendations
22 on safety and efficacy.

23 Remember that, although there's been a lot
24 of comment about how few drugs have been approved for
25 lupus over the last 25 years, that the pipeline is

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1 actually fairly rich right now with a host of
2 biologics and small molecules and alternative
3 regimens.

4 So what happened for the last 25 years is
5 not what's going to happen for the next ten years, for
6 certain.

7 I'm not sure where I come out on this,
8 frankly. Like everybody else, I straddle the fence,
9 but the statistical arguments certainly are
10 persuasive, if we are to remain true again to the
11 charge that this particular committee has.

12 ACTING CHAIRMAN HARRIS: I think those
13 comments are indeed very appropriate, because I think
14 we are all sort of sitting on the fence here. We
15 recognize that our responsibility is really to look at
16 how the data is used, analyzed, and really to
17 determine efficacy based on the science of statistical
18 analysis.

19 At the same time, you know, there is this
20 sense that, gee, you know, if there is some value
21 here, then are we going to miss on an opportunity? I
22 mean, steroid sparing, for instance, is an important
23 aspect of our management of patients with lupus. If
24 this offers some data to suggest that it may have some
25 positive effect without there being really an adverse

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1 cited, then whether or not one might be swayed to move
2 ahead and recommend its use.

3 I'm on the fence, and really, I was
4 wondering. We have a few more minutes, and the
5 question -- Yes?

6 DR. BULL: While we are still on safety,
7 I wanted us to -- We have not commented or no one has
8 brought up the presentation done earlier by Dr. Wilson
9 on the pharm tox literature and what we have in. Just
10 wondering if we could get some comments from the
11 committee based on her presentation, because there
12 clearly is a positive data with regard to
13 carcinogenicity and, I think, as well we are talking
14 about a population of women that are in their
15 reproductive years, and there were some signals in the
16 animal studies for embryologic effects.

17 Specific to the population, I think we
18 would appreciate some comments from you on that part
19 of the earlier presentation with regard to safety.

20 DR. WILLIAMS: It is going to take a lot
21 more patients than we get out of these studies to
22 answer that question. I think anytime you are using
23 a hormone that can have influence on malignancy, you
24 are going to have to follow them over time.

25 I suspect it will be no worse than hormone

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1 replacement therapy, but that's only a guess.

2 DR. FIRESTEIN: We also deal with in this
3 particular population many, many drugs that have far
4 greater potential for toxicity, I think. That's
5 fairly clear. But in order to really assess it, as
6 you said, we are going to have a much larger exposure
7 for a longer period of time.

8 ACTING CHAIRMAN HARRIS: Well, should we
9 put it differently? Is there enough of a signal here
10 with respect to this particular toxicity to make us
11 say, you know, maybe we should not use or not
12 recommend its use?

13 DR. SILVERMAN: No.

14 DR. LIANG: I think we should stop
15 flagellating ourselves, because it's never knowable at
16 this point. I've never seen a drug or heard of any
17 drug where you could tell. I mean, look at the
18 estrogen story for normal women.

19 You know, it was du jour until this past
20 couple of years. You know, we just really have a hard
21 time answering these questions. So I don't think it's
22 knowable.

23 I think, if you look at post-menopausal
24 hormone use, which is much more widely used, we still
25 don't know the answer to that.

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1 ACTING CHAIRMAN HARRIS: One question I
2 did have to Dr. Wilson was whether or not in the
3 animal studies there were effects of DHEA that were
4 over and above what one might expect for any hormonal
5 effect.

6 In other words, the DHEA effects -- were
7 they what one would predict for, say, estrogens and
8 estrogen use in these particular animals or any other?

9 DR. WILSON: In general, I think the
10 things that we did see in the studies, and they were
11 limited -- so a lot of what I'm going to say I am
12 pulling from the literature as well. I think that we
13 did see effects that would be anticipated and were
14 associated with hormonal effects.

15 As to the relative potency of DHEA
16 compared to the estrogens and the androgens, it does
17 not appear to be as potent. That's not unanticipated,
18 because if you are giving 50 milligrams of DHEA, it's
19 going to be metabolized to a number of different
20 routes, and these are include both androgens and
21 estrogens.

22 So it's not going to be expected to have,
23 say, the same potency as giving 50 milligrams of
24 androgen. Did I answer your question?

25 ACTING CHAIRMAN HARRIS: Yes, it did. In

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1 fact, there is one other comment to make. My
2 understanding was that: Suppose again one were to go
3 ahead and approve this. Presumably one would use the
4 same warning as one would for any hormonal replacement
5 therapy or the like. I mean, would that --

6 DR. WILSON: Well, I think we need to have
7 some further discussions as to the exact nature,
8 whether we would have a warning versus a black box or
9 both. I think it's appropriate to use the labeling
10 for estrogens and androgens for the DHEA.

11 ACTING CHAIRMAN HARRIS: Dr. Brandt.

12 DR. BRANDT: Yes. To change the topic back
13 to steroid sparing, there's something I'm not clear
14 on, and perhaps I should be.

15 From the standpoint of a clinician
16 treating lupus, indications for upping the dose of
17 steroid -- well, significant serositis, pericarditis
18 or pleurisy or sudden blindness or flaring renal
19 disease. These are things that most clinicians
20 wouldn't argue about. This would be an indication for
21 them to do something with the steroid dose.

22 When we speak about this drug being
23 steroid sparing, have we taken into account -- and we
24 didn't have an algorithm for escalation. I'm aware of
25 that. Have we taken into account in the data analysis

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1 the frequency of such events in the course of the
2 individual subjects, and where the two groups matched
3 with regard to episodes that might have dictated to
4 most clinicians an indication for jumping the dose of
5 steroid?

6 That seems to me a reasonable thing to do
7 if we want to discuss a difference between the two
8 treatment groups with regard to overall steroid dose.
9 Can we get that out of the data?

10 DR. PETRI: I'm not sure what you are
11 asking about matching patients. Subject patients were
12 randomized. If you are asking just about prednisone
13 sparing, remember that multiple studies, including the
14 Taiwan study, showed a decrease in flares in the
15 Taiwan study, also a decrease in the time to flare.

16 So I don't think we are just talking about
17 prednisone sparing. We are also talking about
18 stabilizing the disease so the patients don't flare as
19 often.

20 DR. BRANDT Right. Were the number of
21 flares in specific organ systems such as those I've
22 mentioned different in the two groups? Were there
23 fewer of those events that might have led clinicians
24 to --

25 DR. PETRI: In 95-02 there were fewer

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1 flares. They did not reach statistical significance.
2 It was in the Taiwan study that the fewer flares and
3 the time to flare reached statistical significance.

4 ACTING CHAIRMAN HARRIS: Well, I think we
5 are slowly winding down here. We are all in somewhat
6 of a state of uncertainty, but of course, can always
7 throw it the way of the FDA.

8 I hope -- I would perhaps -- I'm tempted
9 to ask the committee one more time if they think that
10 the data shown with all its modifications and so on is
11 persuasive enough to say that this agent is something
12 that is worth using, effective, understanding the
13 differences between efficacy and effectiveness, if
14 this is something one would feel relative comfortable
15 recommending its use in patients with systemic lupus.

16 This is nonbinding. This is nothing. I
17 just want to -- because we have heard a lot of
18 discussion this afternoon, and really, we know that if
19 one is a purist in terms of where we would want to go
20 in analyzing this data, the case for efficacy is --
21 but we believe there is something there.

22 Is the belief strong enough that one would
23 say, look, this might be an agent that we might
24 recommend its use in patients with systemic lupus and,
25 of course, given all the other things, SLEDAI>2 or

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1 whatever, we would recommend its use?

2 DR. TILLEY: Could I ask just a quick
3 point of clarification? My understanding is this is
4 being considered as an orphan drug. Are there other -
5 - Are there criteria that one uses in considering an
6 orphan drug? Is there any difference in the criteria
7 than in a standard drug application?

8 DR. BULL: Orphan drug status is typically
9 given to drugs in which the incidence is under -- I
10 believe the magic number is 250,000 patients. So in
11 terms of there being a relative paucity of patients
12 available to study, it does impact on study design.

13 I think looking at the small numbers in
14 the studies that you have before you, I think it does
15 factor into, I think, what has been described as the
16 01 study being in some ways exploratory, that you got
17 the signal for the SLEDAI>2, that the second study,
18 02, appeared to be confirmatory, and given that there
19 are not large numbers of patients available for study,
20 it does figure in.

21 I think our usual standard is that you get
22 confirmatory evidence in Phase III trials, which may
23 actually be of significance, given that you've got a
24 safety and efficacy profile that may not be -- You
25 know, I think it really is on the table as to whether

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1 or not that's been optimally characterized.

2 That's something we are certainly
3 appreciative of hearing your assessment of the
4 sufficiency of the data that is before you, given that
5 so much of this has been, in a sense, compromised by
6 the lack of an established methodology to study the
7 disease.

8 DR. GURWITH: Could I just comment briefly
9 about this point?

10 ACTING CHAIRMAN HARRIS: Okay. I'm about
11 to call a vote, but --

12 DR. GURWITH: All the more reason.

13 ACTING CHAIRMAN HARRIS: Or for comment,
14 not so much vote.

15 DR. GURWITH: Just to reassure Dr. Tilley
16 about, first of all, about the analysis plan, since it
17 was brought up. Although it was amended -- I mean
18 finalized in April '99, as you said, kind of at the
19 end of the study, it had been under continuous
20 discussions with back and forth. So it couldn't be
21 finalized, because it really was a back and forth
22 process with the agency.

23 Now just to address what you said about
24 orphan drugs and your earlier comments about AIDS. My
25 background is infectious diseases, and so I remember

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1 this very well.

2 This drug, besides having orphan drug
3 status, has Subpart E and Fast Track. Those
4 regulations came largely out of the AIDS experience,
5 the HIV experience, and it wasn't that those
6 regulations or those status are to allow you approve
7 a drug without clinical trials, but it was to look at
8 things with more of a risk/benefit viewpoint.

9 I think one of the words is flexibility of
10 regulatory standards for Subpart E, and lupus is in
11 that same situation. That's why it has those
12 standards. So it's not just that no standards apply
13 for these kind of drugs.

14 ACTING CHAIRMAN HARRIS: Thank you.

15 DR. BULL: I think I need to clarify that
16 just a little bit, that the Subpart E really has to do
17 with a serious disease for which there are unmet
18 medical needs.

19 DR. ELASHOFF: I have some objection to
20 having the question be what do you believe about
21 whether this drug works or not. I think we really
22 ought to stick to what has been demonstrated as to
23 whether this drug works or not.

24 DR. ANDERSON: I have a question about
25 clinical significance versus statistical significance,

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1 because in the second trial that we were looking at,
2 you know, the results -- the major result with the P
3 value of .017, which was that 59 percent of the
4 patients on the drug and 45 percent of the patients on
5 placebo stabilized or improved, which is the same as
6 not getting worse. But that means that 41 percent of
7 the patients on the drug got worse versus 55 percent
8 of the placebo patients.

9 I was wondering, you know, if you turn it
10 around that way, how those percentages compare with
11 what might happen in practice over a year for a
12 patient who had a SLEDAI of greater than 2. What
13 percentage of those patients would ordinarily get
14 worse by the criteria in the study?

15 That's probably not known with any
16 precision, but if clinicians who do treat lupus
17 patients have any sort of feeling around this, any
18 sort of impression about this, I would be interested
19 to hear it to sort of help gauge the significance of
20 these findings, the real significance.

21 ACTING CHAIRMAN HARRIS: Dr. Petri, I'm
22 going to ask somebody -- one of our people around the
23 table, feeling that -- if there is a comment. Matt?

24 DR. LIANG: My comment is to ask Dr.
25 Petri.

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1 ACTING CHAIRMAN HARRIS: Dr. Petri, let's
2 go.

3 DR. PETRI: No one has used this responder
4 definition in a longitudinal cohort study. However,
5 I can tell you about flare rates. An average lupus
6 patient in my cohort flares once a year. Now those
7 flares differ in severity. About 50 percent are
8 moderate, 25 percent are mild, and 25 percent are
9 severe. Very simply, that 25 percent are severe means
10 the patient gets hospitalized.

11 The 50 percent that are moderate, their
12 prednisone goes up significantly, by 10 milligrams or
13 more. The mild patients get by with a Medrol dose
14 pack, a triamcinolone injection or a very small
15 increase in their prednisone.

16 So that's what happens to the average
17 patient. So if you can prednisone spare or prevent
18 any of these flares, not only does the patient do
19 better in the short term, you are going to spare them
20 some of that long term steroid toxicity.

21 ACTING CHAIRMAN HARRIS: Can I just ask
22 Dr. Elashoff one question. Certainly, you asked
23 whether or not something was demonstrated, and the
24 question is -- Something was demonstrated if you did
25 a lot of manipulations of the data.

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1 The question is, you know, that given
2 those manipulations, something was demonstrated. And
3 the question is really the acceptability of accepting
4 what was demonstrated with the manipulations that took
5 place. I mean, how comfortable is one in accepting
6 what it is that it showed?

7 DR. SILVERMAN: Another way to look at the
8 data would be: Would it be acceptable to the
9 committee if ten percent of your patients decreased
10 the number of flares they had, which is really the
11 difference ballpark number between the placebo group
12 and the treated group in the second study?

13 So if ten percent of your patients had
14 fewer flares per year, would you be happy, over the
15 placebo? I think the question I would -- It's not
16 what you want, but remember, when you compare lots of
17 other studies, you know, some of the RA studies are 40
18 percent versus 25 percent median response are in the
19 same similar ballpark.

20 So I think in a disease where we don't
21 have a lot of other treatments that, if we can
22 decrease ten, 15 percent of patients per year flaring,
23 that's not bad.

24 DR. JOHNSON: It sounds like there's two
25 issues going around here. One is the relevance vis a

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1 vis the rest of the armamentarium. But the other is
2 the inferential strength of what's going on.

3 I think not all demonstrations are the
4 same, unfortunately. When you start going down a
5 hierarchy, you can call these things nominal P values,
6 but that's sort of a euphemism, and nobody really
7 knows what a nominal P value is, because you can't
8 calculate, you can't quantitate or you can't prove or
9 disprove whether bias has been injected, and you
10 couldn't quantify it, even if you knew the answer, one
11 way or the other.

12 DR. LIANG: May I ask a question? This is
13 -- Again, all decisions, I think, have a context, and
14 this is the largest, I believe, lupus trial ever done,
15 controlled trial ever done. Isn't that true? I think
16 there's never been 300 patients.

17 In any case, if this doesn't get approved,
18 I assume that the company goes belly up. If they
19 don't manufacture this, there will never be anymore
20 studies of this sort on this kind of drug, I would
21 imagine. We'll never get any evidence -- we'll never
22 get any information on toxicity. Is that not part of
23 the context?

24 ACTING CHAIRMAN HARRIS: Yes, but Dr.
25 Liang, I think --

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1 DR. LIANG: Is it fair?

2 ACTING CHAIRMAN HARRIS: Yes. That
3 doesn't need an answer, because I think -- because
4 that isn't sufficient reason, I think, or should be a
5 primary reason in terms of making the decision that we
6 must.

7 In other words, I think in terms -- The
8 survival of a company should not be sufficient in
9 terms of making --

10 DR. LIANG: I'm sorry. I was being cute
11 about that. But basically, it will be off the table.
12 But I think it's -- See, if all decisions were paint
13 by numbers and we did the statistical rigorous route,
14 it would be probably easy, and we would probably be
15 suspended in uncertainty forever in this instance.

16 I'm just saying, if you admit some context
17 into the decision making, what isn't admitted into it?
18 I'm just trying to understand this, because you are
19 going to ask us to vote, and I can't do it by the
20 numbers approach. It's a much more complex issue in
21 this instance.

22 DR. BULL: As a point of reference, if you
23 go to the clintrials.gov site that's done out of the
24 National Library of Medicine, there are 18 trials
25 ongoing that they list in lupus.

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1 DR. LIANG: With 300 people?

2 DR. BULL: I don't know, but I mean to say
3 that this blunts research -- I mean --

4 DR. LIANG: No, no. I meant on this
5 agent. See, I think that -- I mean, it seems to me
6 that if this is removed from consideration, if it's
7 not going to be approved --

8 DR. BULL: What I heard you say, it seemed
9 to imply that it will just blunt research efforts in
10 this area altogether.

11 DR. LIANG: No, no, no. This ongoing
12 research. I think it just means that there's some
13 questions that are meaningful that we can't answer
14 with any kind of 300 sample in lupus -- you know, the
15 toxicity, the long term effectiveness of the drug,
16 other subsets that might benefit.

17 So once we take it -- we remove that,
18 there will never be any studies of this sort or
19 resources to do it as well. We have already done,
20 perhaps in some people's view, a very expensive, time
21 intensive pilot to give us better information on how
22 to do trials in the future, but it's not going to
23 happen very often. It's a lot of patients and a lot
24 of time.

25 ACTING CHAIRMAN HARRIS: You know, I hate

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1 calling for a show of hands, because it really may not
2 be very meaningful where we are really not sure
3 ourselves as to where we come down.

4 That having been said, can I ask whether
5 or not, in the opinion of the committee, -- this is
6 for a show of hands -- there has been demonstrated,
7 given that you are comfortable enough with some of the
8 modifications that had to be made to the data to
9 demonstrate some form of efficacy, that what came out
10 of that is sufficiently meaningful to recommend that
11 this drug be used in patients with lupus?

12 If you want to rephrase it, then --

13 DR. JOHNSON: Nigel, you don't have to
14 feel impelled to vote, I don't think. I mean, if it's
15 appearing overwhelming, I don't think that's
16 necessary. But I mean, it's whatever you want to do.

17 DR. BULL: We are quite satisfied with the
18 answers we have gotten to the questions that we posed.

19 ACTING CHAIRMAN HARRIS: Then I prefer to
20 avoid a vote, because I think we would be probably
21 split. As long as you've -- We are advisory, and I
22 think that as long as you have gotten the information
23 you need, I think then that's where we are going to
24 be.

25 Dr. Tilley, your hand is always forward

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1 and then -- Okay. No, no, I'm not reproving you.

2 DR. JOHNSON: I think we've gotten an
3 incredible amount of very useful feedback already from
4 the committee.

5 ACTING CHAIRMAN HARRIS: That having been
6 said, I wish to thank all of you for what was a very
7 thoughtful afternoon. I declare the session closed.

8 (Whereupon, the foregoing matter went off
9 the record at 4:27 p.m.)

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Before: FOOD AND DRUG ADMINISTRATION
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Date: THURSDAY, APRIL 19, 2001

Place: ROCKVILLE, MARYLAND

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

Rebecca Davis