

1 DR. MERCURI: That is presently in the literature.
2 That is the only number that has been able to be dug out of
3 the literature to use as a standard.

4 DR. HEFFEZ: I understand it is present in the
5 literature. I just wonder of its validity and then relying
6 on a percentage of that number that is calculated, perhaps
7 on a number that is maybe not very valid.

8 DR. REKOW: This is Diane Rekow. Leslie, the
9 300 pounds, I think, is from Charlie Gibbs' article and he
10 did a measurement with transducers for it. But then the
11 distribution of muscles, as I understand it, was based on
12 this Costra article with a finite-element analysis based on
13 muscle mass and direction.

14 Is that accurate?

15 DR. MERCURI: Yes.

16 DR. HEFFEZ: I just wonder about the accuracy of
17 that study and then to rely on 50 percent of the number.

18 DR. LI: I have one question either for the FDA
19 presenters or the company. In the earlier clinical trial
20 with the 363 TMJs and the 215 patients, I couldn't quite
21 tell from the documentation, but were all the implants, in
22 any clinical series, ethylene-oxide sterilized polyethylene
23 or, historically, did they change from one--were they gamma
24 at some time and then switches to ETO or were they always
25 ETO?

1 MR. ROSE: Greg Rose. All these implants were
2 shipped in the non-sterile condition and recommended for ETO
3 sterilization at the hospitals. To our knowledge, that has
4 been the only technique that has been used.

5 DR. JANOSKY: We are going to continue with the
6 FDA presentations. Dr. Pannapolli.

7 DR. PANNAPOLLI: My name is Murty Pannapolli. I
8 am going to give you a review of the statistical aspects of
9 this study. As you know by now, there are two clinical
10 studies here or, more appropriately, two analyses of a
11 clinical study.

12 In the first one, there are 215 patients with 363
13 temporomandibular joints. The study was made by eight
14 different surgeons. The data on efficacy variables and
15 safety were collected up to 48 months.

16 In clinical study No. 2, the number of joints is
17 195 and the number of patients is 111. The data on efficacy
18 variables were collected up to 96 months so there is more
19 follow up in study No. 2. The primary efficacy parameters
20 are reduction in pain measured in 55 millimeter VAS and
21 maximal incisal opening in millimeters. The secondary
22 efficacy parameters are jaw function in 55 millimeter VAS
23 and diet restriction in 55 millimeter VAS.

24 The first study No. 1 reveals the following
25 results. To start, preop, there were 205 patients. The

1 mean pain level turned out to be 42.2 with a standard
2 deviation of 11.6. This is for pain. For opening, there
3 were 198 patients with a mean opening of 24.2 and an
4 standard deviation of 10.6. And so on.

5 It goes up to four years. An important point to
6 note here is the following. In the second row, for example,
7 the 104 patients in the second row does not contain the
8 number of patients in the third row, 70 patients in the
9 third row. Some patients in the third row are in the second
10 row. Some patients in the second row are in the third row.

11 In other words, we don't have a single cohort of
12 patients observed over time. What we would like to know is
13 whether the pain is decreasing, say up to a certain point,
14 to one year or two years. It is not comparing preop with
15 four years, comparing preop, for example, with one year. It
16 is only pairwise comparisons, what we are interested in.

17 One more point I would like to make at this point
18 is even for pairwise comparisons, for subjective
19 measurements, non-parametric tests are better than the T-
20 test because subjective measurements are relative. If a
21 patient says at 12 months that he does not have pain is,
22 like I say, 20 and, at four months, 30, it is only relative.
23 Time levels, taken by themselves, are not very accurate.
24 All we can say is at 12 months, it is less than at four
25 months.

1 In study No. 2, there are similar observations for
2 pain and opening. We have, again, the same problem. The
3 cohort for patients is not observed over time. But at my
4 suggestion, what the sponsors did was, one year is a typical
5 level time point to observe. At 12 months, the pain level,
6 for example, is 69, 18.5. And these observe the pain level
7 of the very same 69 patients at preop. I found, in the
8 Wilcoxon Signed Rank test, to see if there is a direction of
9 pain at 12 months.

10 It turned out when we performed this test, the p-
11 value turned out to be less than 0.0001 which indicates that
12 the pain level went down, really, at 12 months compared to
13 preop. A similar thing holds for opening. At this time,
14 the opening has increased rather than decreased.

15 Next is the question of survival probabilities,
16 how long does the device last, roughly speaking. It depends
17 on the definition of failure. Originally, the sponsors did
18 came up with an acceptable definition of failure, but later
19 revised the definition.

20 According to the first definition of failure, the
21 last two columns in this table are the most important. At 1
22 year, the cumulative probability of survival--which is to
23 say the probability of survival to 1 year--is 0.90. It is
24 an estimate from the so-called Kaplan-Meier estimate which
25 is a very good way of estimating with confidence intervals

1 of 0.84 and 0.96.

2 The confidence interval involves the variance of
3 the estimate. And that is obtained by the so-called
4 Greenwood formula. At two years, the probability of
5 survival to two years turned out to be 0.75 with the
6 confidence intervals of 0.67 and 0.84. At four years, it
7 was 0.75 with confidence intervals of 0.67 and 0.84.

8 According to the data updated, as of 4-1-99, the
9 estimate for the cumulative probability revised, as I
10 already pointed out, the failures have changed. It is very
11 different as one might expect. What do we mean by failure,
12 which is, what do mean by survival?

13 According to the new definition, according to the
14 updated data, those three values of survival probabilities
15 at one, two and four years turn out to be 0.99, 0.9723 and
16 0.9723 with the corresponding intervals as 0.97, 1.0, 0.94,
17 1.0 and 0.940, 1.0.

18 The survival probabilities I just mentioned were
19 in study No. 2. The corresponding properties in Study No. 1
20 at one, two and four turn out to be 0.9229, 0.9229 and
21 0.8730. The corresponding intervals are corresponding to
22 one, two and four. Notice that, at four years, the number
23 of patients I would say the last interval, the last point
24 estimate, is not as reliable because that number is very
25 small.

1 Are there any covariates that influence the
2 postoperative scores of pain function in the opening? A
3 multiple regression analysis was done to study this and the
4 covariates studied were age, TMJ duration, prior surgeries,
5 sex, trauma, left prosthesis, right prosthesis, baseline
6 values.

7 It turns out pain--I will go through them one-by-
8 one. The covariates that influence the outcome of pain were
9 prior surgeries and trauma, trauma yes or no. There are
10 only two values. The covariates that influence functioning
11 are the number of prior surgeries. That is the only one.

12 The covariate that influenced the opening--there
13 are two of them, again--are number of prior surgeries and
14 the baseline opening. This is from study No. 1.

15 For study No. 2, the same type of multiple
16 regression analysis was made and it turns out there are no
17 covariates that influence the pain but, for function, it is
18 trauma and baseline. For opening, it is just the baseline
19 value.

20 I thought I would give the details of this
21 Wilcoxon Signed Rank Test which is the nonparametric test I
22 referred to since the above test compares the two variables
23 on the same 66 patients. A reasonable conclusion from both
24 p-values is that pain and function decreased and the opening
25 increases from preop to one year.

1 The type of pairwise test that Dr. Mercuri
2 referred to are from a T-test. By the time it was to four
3 years, I think it is, the number dropped down to six in
4 study No. 1. That means that the pairwise T-test compared
5 only six pairs. They took the preop values of these six
6 people and that means there are only six pairs. So the
7 paired T-test, for one thing, we only have values, a
8 subjective parameter.

9 And there are too many tests. This is so-called
10 multiplicity of tests which is a statistical problem.

11 My final comment. The data to compare the outcome
12 variables simultaneously at several time points are not
13 available in this submission. A way to do this is to
14 observe the variables in a cohort of patients and use either
15 repeated measures ANOVA F-test or a nonparametric test.
16 Pairwise comparisons at different time points, as I already
17 mentioned, lead to multiplicity of tests.

18 Two, as I already mentioned, pairwise T-tests are
19 less reliable than nonparametric tests, particularly for
20 pain and function, since the preop and postop levels are
21 only relative.

22 Three, of patients who are better off or worse off
23 have a tendency not to return for follow up, this introduces
24 bias in the comparisons of outcome variables on different
25 sets of patients.

1 Thank you.

2 DR. JANOSKY: Questions from panel members for Dr.
3 Pannapolli or Dr. Runner or Ms. Blackwell?

4 DR. PATTERS: Dr. Pannapolli, it would seem to me
5 that the key issue here is the high number of patient losses
6 and whether or not the existing patient data can be
7 extrapolated to all patients that were treated or not. Is
8 there any way to get a better handle on that because I think
9 it is a critical determination as to whether the 69 patients
10 that all data are available on are actually a biased subset
11 or, alternatively, clearly reflect the population.

12 Any way to get a better handle on this?

13 DR. PANNAPOLLI: As you can see, the only way--if
14 we have the pain levels of all the patients at 12 months,
15 pain levels of all the patients, preop, if I understand
16 correctly, we don't have that data. Some are missing. If
17 there are too many are missing at any particular level, that
18 is bad. We cannot perform a statistical test. It is
19 difficult. What we would be essentially testing is the mean
20 of the subset is equal to the mean of the whole population.
21 That is difficult.

22 But we can examine if they are close to the mean
23 of the whole population values, as many of the population
24 values as we can get.

25 DR. PATTERS: Would you agree that that is

1 critical in interpreting the data?

2 DR. PANNAPOLLI: If you pretend that that the
3 experiment was done only on 69 patients, which is a small
4 number, it is not too bad. What can we do if the data are
5 not available?

6 DR. ALTMAN: I am just a little bit confused--
7 well, probably a lot confused, but the question on the
8 third-to-the-last page of your handout, at the very bottom
9 where you said the prior surgeries and site of the
10 prosthesis are not important predictors? Didn't we hear
11 earlier that that was a predictor?

12 DR. PANNAPOLLI: Are you referring to the last-
13 but-one page?

14 DR. ALTMAN: Third-to-the-last page, at the very
15 bottom, your comment on there on study 2. Is that not
16 contradiction from what we--

17 DR. PANNAPOLLI: It is. It seemed to me I did not
18 have all the data. It does contradict. It is puzzling. I
19 might call it one of the vagaries of statistics because I
20 don't have all the data to examine that and I cannot think
21 of any possible explanation of this discrepancy.

22 DR. LI: Did you look for any correlations with
23 device performance, for instance, with physician? In other
24 words, you only had a relatively few number of physicians
25 here. Was the data biased to any one particular physician

1 and, as a follow-up question, did you also look at the
2 performance of the device, as a function of some device
3 features.. For instance, did those devices that use more
4 screws have more pain or did those devices that had thinner
5 polyethylene than thicker have more pain?

6 DR. PANNAPOLLI: The answer to the second question
7 is no. What was your first question?

8 DR. LI: Was there a surgeon dependence on the
9 outcome?

10 DR. PANNAPOLLI: I have reason to believe,
11 although I have not examined it thoroughly, that, for a
12 couple of physicians, the way their patients scored the pain
13 levels seemed to be different. You see, it is subjective.
14 If you and I have pain, you may score it as 40 and I may
15 score it as 20. That is possible.

16 So I have reason to believe that for a couple of
17 physicians the patients scored the pain consistently higher.

18 DR. LI: My question was more aimed at Dr.
19 Mercuri's earlier comment that there was a learning curve
20 that they went up early on in this device. I guess my
21 question is did some surgeons never go up that learning
22 curve?

23 MS. BLACKWELL: This is Angela Blackwell to
24 comment on the learning-curve thing. I believe most of the
25 learning curve was with the company and not with the

1 physician. It was a manufacturing learning curve as opposed
2 to a clinical.

3 DR. LI: Did you look for a surgeon factor in the
4 outcomes? Have you looked at the data?

5 MS. BLACKWELL: The reason the dataset for
6 clinical study 2 was done was because those two physicians
7 had more follow up. We actually requested that in the
8 510(k) because when we looked at the whole subset,
9 originally, we saw just clinical study 1. When we looked at
10 that, there was a trend that two of the clinicians had more
11 datapoints than the other six. And that is why they were
12 pulled into a subset.

13 DR. LI: I understand that. I guess I am trying
14 to figure out if those two surgeons had a difference in
15 performance of the device than the other six?

16 MS. BLACKWELL: There didn't appear to be a
17 difference in the data, no--just in missing data, not in the
18 data--

19 DR. LI: But you did look for that, though, a
20 surgeon dependence?

21 DR. JANOSKY: Would someone from TMJ Concepts like
22 to respond?

23 DR. MERCURI: Louis Mercuri. I actually did look
24 at the difference between Dr. Wolford's patients and my
25 patients and compared them and there was no difference in

1 them. This was a homogenous cohort.

2 DR. JANOSKY: Any additional questions for the FDA
3 presenters?

4 DR. PATTERS: To go back to Dr. Altman's question
5 again, the fact that study 1 shows that number of prior
6 surgeries has a very strong agreement with the amount of
7 pain reduction, inverse agreement with the amount of pain
8 reduction, and the subset of that data, study 2, says that
9 it doesn't, does that suggest that study 2 is a biased
10 subset of the total population?

11 Did you want me to repeat that? Study 1, as I
12 understand it, shows that there are a number of prior
13 surgeries where there is a very strong inverse correlation.

14 DR. PANNAPOLLI: Right.

15 DR. PATTERS: Study 2, which is a subset of study
16 1, does not show that. Does that suggest, then, that the
17 subset which comprises study 2 is a biased subset of the
18 total population?

19 DR. PANNAPOLLI: Yes. This ends up a bias with
20 this respect, with respect to number of prior surgeries.
21 Yes.

22 DR. PATTERS: I think that was a yes. Thank you.

23 DR. JANOSKY: I actually have a follow-up question
24 concerning Dr. Patters' question, Dr. Pannapolli. Is that
25 an issue of bias or is that an issue of power? Was the

1 power tested for that linear regression model for the second
2 presentation?

3 DR. PANNAPOLLI: Yes, but you can't predict it so
4 much if it is a question of power. It is in total
5 contradiction.

6 DR. JANOSKY: Exactly, the directionality is. But
7 one of my concerns, and I will touch on this a little later,
8 is that once you take that subset down, you are still only
9 dealing with essentially 66 subjects, or 66 patients.

10 DR. PANNAPOLLI: That is a possibility; yes. You
11 cannot conclude--the term "bias" is very vague. I agree
12 with you. It could be due to lack of power. You could say
13 due to lack of power, we got a bias.

14 DR. JANOSKY: There you go. You sort of marriage
15 the two concepts.

16 DR. PATTERS: Dr. Janosky, if you could maybe help
17 me a little bit. If it were a lack of power, would one
18 expect the p-value to go from 0.002 to 0.83? Could that be
19 explained by power alone?

20 DR. JANOSKY: Let me take a look at what you are
21 looking at. Just pull it up here in front of me.

22 DR. PANNAPOLLI: That is what it is, a total
23 contradiction.

24 DR. JANOSKY: I don't think that could be
25 accounted for by power alone, but one of the issues that I

1 see creeping in there that, hopefully, later I will have a
2 chance to address some of these issues, is what happens when
3 you chop, chop, chop this group to essentially a very small
4 group? So, no; I agree that it is not most likely power
5 alone but I think that power is part of it, power and bias
6 together.

7 DR. PANNAPOLLI: Right. It could be both, due to
8 power and bias.

9 DR. JANOSKY: Just sort of for my own mind, what
10 we are essentially talking about when we get to that second
11 dataset is relatively complete data on 66 patients for one
12 year of follow up, end of story; is that correct?

13 DR. PANNAPOLLI: Correct.

14 DR. JANOSKY: So anything past that gets to be on
15 very uncertain grounds, anything past 12 months.

16 DR. PANNAPOLLI: But you should remember, the
17 patients say at two months and four months.

18 DR. JANOSKY: Right.

19 DR. PANNAPOLLI: They do not contain all these 66.
20 They are different. At any time point, the set of patients
21 is different from set of patients at any other time point.

22 DR. JANOSKY: So we are essentially looking at
23 different groups of patients even at different time points
24 with a fair amount of missing data.

25 DR. PANNAPOLLI: Exactly.

1 DR. JANOSKY: Thank you.

2 Would you like to reply to that discussion?

3 DR. MERCURI: Yes. There are two issues I would
4 like to respond to. Number one is the issue of a different
5 dataset. The reason that the ANOVA with repeated measures
6 was done was to see if there was a repeatability or a
7 sustainability of effect in study 2 over the study period.
8 I believe I presented that data that showed that, according
9 to the regression lines, that there was a sustainable effect
10 in pain and function. So I think that may respond to that
11 question.

12 The second question I would like to respond to was
13 the issue of the number of surgeries that were done. If the
14 panel, and I'm sorry I don't have an overhead for this one
15 but I do have an overhead for study 2--but in study 1, on
16 page 0865, we have graphs showing 0 to 4 surgeries, 5 to 9,
17 and 10 or more surgeries.

18 And then I have an overhead of study 2. I would
19 like to address the issue of bias in this. I think there is
20 a power effect here. For the sake of time and complexity,
21 can we just look at figure No. 10 in study 1 and this
22 figure. Again, I am sorry that we don't have an overhead
23 for this, but this shows what I was talking about before,
24 the problem with the number of prior surgeries that a
25 patient has.

1 The closed diamonds represents 0 to 4 surgeries.
2 You can see that those patients did very well. I would like
3 you to forget the 84 here. This is a small number of
4 patients but let's track it to 72 months. The filled square
5 is 5 to 9 surgeries. You can see that those patients did
6 not do nearly as well.

7 And then when we take the open triangle, which is
8 10 or more surgeries, we can see, as they track along, they
9 did not do nearly as well. So it is dependent on the number
10 of surgeries. It may not be as statistically significant as
11 it was in study 1 which is in figure 10, but the
12 reproducibility of this data, based on this subset which we
13 have already agreed was a subset of the total cohort and had
14 some reproducibility, I think shows what we were talking
15 about here.

16 Again, I am not a statistician. I apologize for
17 my inability to articulate that, but, as a clinician,
18 looking at these data in this manner, I think it shows
19 reproducibility.

20 DR. JANOSKY: One of the issues, just to address
21 your first comment, if we think about--you made the
22 statement a couple of times in your presentation and here
23 also that past 12 months, you don't see a change, where
24 there was no significant difference across time in terms of
25 pain, in terms of--what was the other concept that you were

1 talking about?

2 DR. MERCURI: Function.

3 DR. JANOSKY: Jaw function. And that gets back to
4 the issue I had just asked previously is was it a power
5 issue, though, because even once you get past the 12 months,
6 the number of patients that you have data on is quite small.
7 So, if we say we have no significant differences, one of the
8 conclusions I could possibly make is you just didn't have
9 enough power to pick something up.

10 So, can you differentiate between those two
11 possible conclusions?

12 DR. MERCURI: I have another set of data.

13 DR. JANOSKY: If it is very short presentation.
14 Is it going to be something we had seen before?

15 MS. BLACKWELL: Dr. Pannapolli's suggestion on his
16 last page.

17 DR. JANOSKY: Ms. Blackwell, you are talking about
18 this, the recommendations?

19 MS. BLACKWELL: Yes. I am a little bit ahead.

20 DR. JANOSKY: That actually is the issue that I am
21 trying to address.

22 MS. BLACKWELL: Yes; they have some of that.

23 DR. MERCURI: These data represent 34 of the
24 patients that had a complete dataset in study 2. This slide
25 was prepared in response to the review by the statistician,

1 Dr. Pannapolli. We have now taken the 34 patients, of the
2 69 patients from study 2, that had the best follow up. We
3 now have datapoints at each one of the intervals up to
4 36 months.

5 Again, we are seeing the same reproducible graph
6 over the time period of three years. And the same thing
7 happens with the objective data.

8 DR. JANOSKY: Do you happen to have that graph
9 with error bars on it? Do you have a version of that graph
10 that would show error bars around each of those time--

11 DR. MERCURI: We have the standard deviations.

12 DR. JANOSKY: Again, those are not the same
13 patients, necessarily, at each of those time points; is that
14 correct?

15 DR. MERCURI: That is the same patients.

16 DR. JANOSKY: But you have dropout; is that true?

17 DR. MERCURI: Here are the numbers.

18 DR. JANOSKY: Is that the entire 69, all the way
19 to the end?

20 DR. MERCURI: It is 34 from beginning to end.

21 DR. JANOSKY: So you are taking the number of 200
22 or something and we are all the way down to 34 with complete
23 data; is that correct?

24 DR. MERCURI: Yes. I have mentioned why the
25 dropout rate is as it is, and I will not reiterate.

1 DR. JANOSKY: So that goes back to the issue I was
2 raising about do you now have enough power. Was there a
3 power analysis done to see whether you are really finding no
4 change in pain, no change in jaw function, due to lack of
5 power or due to truly no change?

6 DR. MERCURI: To answer your question; no.

7 DR. JANOSKY: You just haven't done that analysis.

8 DR. MERCURI: That's correct.

9 DR. JANOSKY: Okay.

10 DR. HEFFEZ: What was the repeat-surgery
11 distribution in that group of 34 patients, Dr. Mercuri?

12 DR. MERCURI: I can't tell you that.

13 DR. JANOSKY: Any additional panel questions for
14 FDA at this point?

15 **Open Committee Discussion**

16 **Presentations by Panel Members**

17 At this point, I would like to move into the open
18 committee discussion. Within the open committee discussion,
19 we are going to hear from two panel members. The first is
20 Dr. Diane Rekow and the second one will be Dr. Leslie
21 Heffez--Dr. Richard Burton; excuse me. We have been going
22 back and forth on this.

23 Let me repeat myself. In the open committee
24 discussion, we will hear first from two panel members, the
25 first being Dr. Diane Rekow, the second one being Dr.

1 Richard Burton. After that time, then I would like to
2 around the panel and address particular questions that each
3 of the panel members might have.

4 DR. REKOW: This is Diane Rekow. The company was
5 asked, as I read this information, in 1995 to respond to a
6 number of questions. Most of them were addressed quite
7 adequately but there are some that I still have a little
8 trouble with and I want to address three of those questions
9 specifically, and then I have a couple of other general
10 comments.

11 In question 7(d), an explanation was requested for
12 why the fatigue testing was performed in air and at room
13 temperature with an angulation and a load of 150 pounds.
14 The angulation and the load, I think, was adequately
15 described but the response regarding the environment was, as
16 I quote, "We don't believe that performing the test in an
17 aqueous environment at body temperature would affect the
18 results in any way."

19 There was no rationale or explanation or
20 references provided. I have a suspicion, and Dr. Li
21 probably knows the literature better than I, but there may
22 be some--and at least a reference in the literature that
23 would support that belief would have been helpful.

24 My biggest concern is really relating to the wear
25 test. A finite-element model was used and calculated a load

1 of 16.82 kilograms. Literature suggests that loads could be
2 much higher and the tests were done at 9 kilograms. A
3 request was made to justify the load based on information in
4 the literature. The response was that the joints are not
5 anatomically normal and the forces were reduced because of
6 scarring and previous surgeries, which is certainly the
7 case.

8 The load chosen is based on "a thorough review of
9 the literature and, to the best of our knowledge,
10 approximates the in vivo loading of the prosthesis." And
11 they reference the Gibbs article which has a maximum force
12 of 8.3 kilograms arguing, also, further, that the forces
13 will be reduced by 63 percent and 33 percent of that figure
14 depending on molar position and the model used, although I
15 didn't find justification for how you got the 63 percent and
16 the 33 percent.

17 And then removing the temporalis and lateral
18 pterygoid will further reduce that. It's true that
19 certainly these are compromised joints. There is no
20 question about it. And then there is some reference to the
21 track record of the material.

22 But what I found perplexing was why you would
23 bother to do the finite-element model and then only use
24 50 percent of the value that you predicted in your own
25 model. So that, in my mind, is still a confusing issue.

1 In the 1995 information, you were directed to
2 either repeat the joint-simulation wear test at a greater
3 load or to provide results using another test method, for
4 instance, a pin-on-disc, at a higher load. Neither of them
5 were done. And this is of particular interest relating to
6 the wear debris that could accumulate and the pathologic
7 reactions, which has come up before.

8 In question 7(h), you were requested to provide a
9 detailed explanation of how an in vivo maximum shear load of
10 25 pounds was established and your response argues that the
11 maximum load can be estimated as roughly equal to the
12 maximum force generated by the muscles that generate or
13 resist forces along the vectors that you show.

14 The forces are based on the predicted values on
15 cross-sectional area and you reference the Costra article.
16 Solving for those gives you a joint axis. And you go along,
17 but you never get to why you use 25 pounds and a safety
18 factor of 3. So I got confused with some of that logic and
19 never could find an answer in the read that I did.

20 The static-strength tests are a little bit of a
21 concern to me. There wasn't any information provided about
22 the number of specimens tested and the raw data, apparently,
23 is no longer available. So we don't know anything about the
24 range and standard deviation for the tests, only the average
25 values. That would have been less of a concern except for

1 when the--no; this is probably not a large issue since the
2 averages that you have greatly exceed any values that we
3 will see as probable loads.

4 But it is a little bit of a concern that there may
5 have been one value that was extremely low or there was
6 something that fractured at a very low value that could be
7 important but would fall out in average data. Again, that
8 is not a big deal, but it is perplexing when the raw data
9 isn't available.

10 I also think that the surfaces and subsurfaces
11 need to be looked at for cracks. I know that you looked at
12 the surfaces, but I think that there is some concern in
13 damage mechanisms that it may occur beneath the surface,
14 especially in the polyethylene and especially under load in
15 a water environment. And that is a concern that still
16 remains.

17 Those are the issues that I have. Thanks.

18 DR. BURTON: Dr. Richard Burton. In my review,
19 there were some things I am going to cover, since we are
20 behind schedule, reasonably quickly. Some of these have
21 already been addressed. I think the first one is the loss
22 of power in the dataset and the fact that you have gone to
23 smaller and smaller, increasingly smaller, subsets which,
24 when I look at the statistics, lead me to come concern about
25 whether we do see changes or we do see differences between

1 various groups that are not addressed because of the small
2 number included within that.

3 I am not sure that the company has adequately
4 addressed why so many of these patients have been lost to
5 follow up. I do clinical trials myself. I know how
6 difficult it is to follow those. However, in this type of
7 study with the type of patient population, it is relatively
8 imperative to try to keep those.

9 It appears, though, that they are trying to
10 address that in their ongoing study now.

11 The second one comes out of the package insert
12 from a clinical standpoint. It talks about the various
13 indications and contraindications for the use of the
14 implant. My question is certainly I think most of the
15 patients met the indications for their use but, again, when
16 we are looking at this type of patient population, whether
17 some of those patients maybe had contraindications to their
18 use and how that can be monitored because two of the
19 contraindications include uncontrollable masticatory muscle
20 hyperfunction, clenching/grinding, which may lead to
21 overload or loosening of the screws and, two, any disorder
22 mental or neuromuscular that may cause the patient to ignore
23 the limitations and precautions in the use and function of
24 the implant.

25 Again, concerning the fact that we have spoken

1 earlier about, the fact that this is certainly a
2 multifactorial type of problem which has a neuromuscular
3 component, again, how that is a contraindication and how
4 that is addressed in the selection of patients for that I
5 think needs to be looked at as we evaluate the product.

6 Also, in the area of failure. Again, you have
7 given some information regarding implant loosening and the
8 loss of those. The question is, again, is that a
9 contraindication and, in fact, is that due to muscular or
10 neuromuscular activity as a component in those patients in
11 which the implant was lost.

12 Secondly, along the failure line, there was a
13 question of is there any stress shielding in the bone
14 surrounding the base of the condylar portion of the implant,
15 whether that may affect its long-term survivability. Again,
16 in those where it has been lost, was there anything done
17 clinically or otherwise looking at the bone underneath the
18 implant when it was removed.

19 You also addressed the fact that there was a
20 learning curve, that early on there were a number of these
21 less--in looking back through and reviewing material, there
22 are obviously some design changes. The question is, at this
23 point in time, do you feel that this is a stable finished
24 product or is it still in an evolutionary stage.

25 I know that both the shape and size of the

1 attachment point to the mandible, the number of screws that
2 are placed, has changed in this evolution and how that has
3 affected, again--obviously, your losses were more in the
4 early group as opposed to the later group.

5 Also, it would be the questions of clinical
6 efficacy I think that would should consider. Again, whether
7 there are functional issues, number one, which were
8 addressed somewhat, I think, adequately in your statistics
9 in terms of range of motion and masticatory function.
10 However, how that relates back to the questions that came
11 from Dr. Altman and Ms. Cowley regarding the clinical
12 efficacy of in terms of pain patients, the suffering
13 aspects, whether the pain complaint was adequately evaluated
14 in these patients postoperatively.

15 Then the last one, your follow up--I know you are
16 looking at 100 percent two-year follow up when, again, you
17 also stated that most of the failures in this seem to be in
18 the three-to-four-year point and how long this dataset would
19 be followed out until completion and, again, the comparison
20 to--I know we have a person on the panel from orthopedics,
21 but how this compares to the long-term studies in
22 orthopedics in terms of length of study to failure.

23 DR. JANOSKY: Would the sponsor like to reply to
24 either of the comments by Dr. Rekow or Dr. Burton?

25 MR. ROSE: Greg Rose to respond to the concerns on

1 the testing. It was regrettable that the raw data was lost
2 from this first test for the wear strength and static
3 strength, but clinically that has not proved to be a problem
4 with these implants so we really haven't looked at repeating
5 any of that type of testing.

6 The same pretty much goes for the wear-test values
7 in that we haven't seen any evidence, clinically, of wear-
8 related problems with particulate matter and many of the
9 analyses that presented the information were done in
10 response to FDA questions for the 510(k) clearances. But
11 most of those things have not been problematic, clinically.

12 DR. REKOW: This is Diane Rekow. I was just a
13 little surprised with the Proplast problem that was really
14 obviously related to wear debris, that you didn't do that.
15 You don't need to justify it.

16 MR. ROSE: But this material has been well-
17 characterized and in use for orthopedics. It was when the
18 device was initially made, the concern wasn't of
19 characterizing a new material. This was considered to be a
20 proved material that had been used, studied out for
21 orthopedic implants, and that was not as much of a focus
22 initially.

23 Also the early comment regarding some of the early
24 failures. This is definitely a stable design. The
25 evolution was to put smaller and a greater number of screw

1 holes in. I believe it is five failures that we have
2 recorded that were involved with implant loosening. We
3 actually do not expect to be repeated. That was five cases
4 out of 111 patients.

5 In the life-table analysis, we saw, that, in
6 recent years, there have been no failures and we actually
7 don't attribute that as an expected failure mechanism to be
8 seen. For example, in the postmarket surveillance study
9 that we are doing, we don't expect to see those percentages
10 recur because that was really attributed to early design
11 evolution.

12 Also, the one dislocation, failure or adverse
13 event that we reported, we modified and added the posterior
14 lift and anterior lift onto the prosthesis and that has
15 prevented recurrences of that adverse event.

16 Thank you.

17 DR. MERCURI: Louis Mercuri to address the
18 clinical questions of Dr. Burton's. Number one, I would
19 like to address the issue of the dropout, maybe from a
20 different angle. Number one, I believe we were too
21 aggressive with a number of data time points that we looked
22 at.

23 As I mentioned before, we were dealing with
24 multiple surgeons, multiple states, patients moving around
25 in multiple states. It is very difficult with the data

1 points at two months, four months, six months, to get those
2 patients to get on an airplane and come back, number one.
3 So I think we were a little too aggressive with that.

4 Secondly, I think a big component of the dropout
5 here is the fact that Sulzer, who was the parent company of
6 Techmedica, decided, for business reasons, to close
7 Techmedica. It had nothing to do with the
8 temporomandibular-joint issue. It was just a business
9 decision on their part. They are from Switzerland.

10 At that point, the study lost its sponsorship and
11 it was very difficult to have these surgeons, including
12 myself and Dr. Wolford, to be able to follow all these
13 patients as closely as if we had a study going that was
14 sponsored. So I think that has to be taken into
15 consideration as well.

16 The other issue that I would like to address is
17 the fact that Dr. Patters asked this morning about the
18 percentage of failures, and I gave a number of 8 percent.
19 When I gave that number of 8 percent, I was talking about
20 the big study, the 215 patients, 363 joints.

21 I would like to characterize the study 2 numbers
22 which show the there were five patients that had the device
23 removed, again early on in the study, which is five of 111
24 which comes out to 5.5 percent. If we look at joints, it
25 was five joints out of 198 joints which, when calculated

1 out, is a 2.5 percent for study 2 which was the closer
2 follow-up study.

3 The fourth thing that I would like to address is
4 the issue that Dr. Pannapolli brought up of failure. What
5 we were considering as failures in the first study. Again,
6 I think from a clinician's standpoint, we were maybe too
7 hard on ourselves and, in the life-table analysis, we
8 included patients, as I alluded to, that we would normally
9 not consider failures.

10 In an orthopedic surgery, a device is not
11 considered failed when the patient asks that it be removed.
12 It was not a problem with the device. It was a problem with
13 the patient. Therefore, I think the definition of failure
14 for study 1 was much different than the definition for
15 failure for study 2.

16 For study 2, we used the orthopedic adverse events
17 definition rather than the definition of failure used in
18 study 1. So I would like to clear that up.

19 Lastly, I would like to say that, again going back
20 to the life-table analysis, that the failures that we showed
21 occurred in the initial stages of the device. I think the
22 question was raised about the surgeons involved. There was
23 a protocol that was developed. All the surgeons were
24 initiated on that protocol so that the variation in
25 surgeons, I don't think, is an issue here.

1 The fact that there were no failures or MDRs that
2 were reported in the past five years indicates that the
3 device has performed satisfactorily.

4 Thank you.

5 DR. JANOSKY: Continuing with the open committee
6 discussion, are there any questions for FDA, for the
7 sponsor, for other panel members?

8 MS. COWLEY: I'm Terry Cowley. I have a question
9 for the company. High-end particulate load from the first
10 bite takes place and, like the first step, it produces a
11 large or small number of particles. In the hip, apparently,
12 they are fairly well contained in the cup portion where
13 isn't the nerve and blood supply as in the TMJ.

14 Do you all know where this stuff is going in the
15 patients? And, to add to that, are you seeing any
16 difference in the patients who have had devices implanted
17 previously and in those in whom this would be their first
18 device, by way of reaction to materials?

19 DR. MERCURI: The first question was do we know
20 what is happening to any particulation. In deference to Dr.
21 Li's response and my response to Dr. Li, as I have shown in
22 our paper, we have not seen particulation. So I can't
23 answer that question.

24 The second question was is do we see a difference
25 in the patients that have never had Proplast/Teflon in place

1 or any other device in place in the rheumatoid patients,
2 which I would have to characterize as the zero prior
3 surgeries. Yes; there is a difference. The rheumatoid
4 patients, as I testified to before, do much, much better
5 than patients who have had previous material failures.

6 MS. COWLEY: Has the company considered using
7 commercially pure titanium instead of the one which includes
8 vanadium and aluminum?

9 MR. ROSE: We do use commercially pure titanium as
10 the backing for the fossa component. The alloy which you
11 refer to is made for the bone screws. They are made out of
12 the vanadium-aluminum alloy. And the mandibular body,
13 itself. That is a much stronger material. Of course, the
14 pure titanium would not exhibit the same strength that we
15 would require in a device like this.

16 MS. COWLEY: I have just heard of the first
17 patient who called us and said she had an allergic reaction
18 to the vanadium and that is why I am asking if there is a
19 problem.

20 May I respond to things said this morning? I
21 would like to address Dr. Bertram's concern about the abuse
22 as a cause of chronic-pain patients and we do not have any
23 data on how many TMJ patients were abused and that they now
24 have this problem as a result of it.

25 However, these patients have suffered an

1 incredible amount of physical and psychological abuse by the
2 dental and bioengineering communities. At this point in
3 time, the psychiatric community really does not deal very
4 well with iatrogenic damage.

5 So I would just like to make that point. The
6 extreme of this damage is--two examples that I will give
7 you. That is the patient in New Jersey whose husband called
8 to tell me she had twelve surgeries, three different
9 devices. They went to the surgeon. He told them that there
10 is absolutely no reason for her pain, she needed a
11 psychiatrist. They went home. The husband asked who should
12 he believe, the surgeon or her; he was the expert. And she
13 promptly went in the bedroom and blew her head off.

14 And another woman who the doctor refused to take
15 her implants out and the pain was so incredibly excruciating
16 that she took all of her pain medication, shot her two
17 children and killed herself.

18 So you better believe we have some psychological
19 trauma going on, but it isn't all from abuse when we were--
20 before we could remember.

21 The problem with follow up, Dr. Mercuri--you know
22 that we hear from an awful lot of patients. You are right.
23 People don't ask us anymore for a "doctor in my city." They
24 say, "Where in the world can we go?" So they do travel.
25 These surgical procedures are costing anywhere from \$30,000,

1 and I have an estimate here for \$101,000.

2 They are terribly expensive and, by the fifth
3 surgery, most patients are bankrupt. Who pays for the
4 patients follow-up treatments? I happen to know your
5 doctors do not--they do charge for these visits. And I
6 happen to know that your other partner in this will not see
7 patients if they actually have a balance on their account.

8 Obviously, the financial status of the patients is
9 to be considered here. If this a "study," isn't there some
10 accommodation that the company is able to make or the
11 surgeons see these patients free of charge. That is one
12 question.

13 I think any patient who is doing poorly, and
14 certainly we know them. They live with emotional blackmail.
15 They don't want the surgeon to know that they have that
16 device out and were lucky enough to get another surgeon to
17 see them and explant that broken device. So I think this is
18 a major issue.

19 I happen to know that one of the patients who had
20 had a Techmedica device, the previous company, she had it
21 explanted, another implant, and she died shortly thereafter.
22 Did she die from your device? Do we say that? Of course
23 not. Was it a progression of this disease? Was it the 26th
24 surgical procedure? We don't know this, but I think these
25 are issues that really need to be looked at.

1 And then let's try to throw a positive on this.
2 How can we change the system that you are in at this point
3 to make it better? And how can all of us work on this?

4 DR. MERCURI: I would like to address these three
5 issues. Let me get them clear. The first issue was the
6 financial aspects of follow up. I cannot speak to the
7 financial arrangements that patients make with other
8 surgeons or who you characterize as a partner. That is
9 their issue. I cannot deal with that.

10 I can tell you that, typically, with surgery there
11 is a global fee involved, and that surgery involves the fee
12 for the surgical procedure, itself, and the follow-up
13 appointments up to a certain period of time. Typically, it
14 is about 90 days. After 90 days, a fee can be charged for
15 follow-up visits. I can't answer more than that on that
16 issue.

17 The second issue was--

18 MS. COWLEY: The patients that are doing poorly.
19 They don't go back to their surgeons for follow up. They
20 just drop off and end up finding another doctor to explant
21 that device and do another.

22 DR. MERCURI: I think, as I brought up in the
23 beginning of my presentation, the profile of this particular
24 group of patients is so completely different from the
25 profile of the average patient that we see for any form of

1 reconstructive procedure.

2 It is an anatomical profile that is completely
3 different. It is a psychological profile that is completely
4 different. I don't know that we have our arms around this
5 problem. And, as I said, in dealing with this thing for ten
6 years, I don't really have my arms around that particular
7 component of this problem.

8 I will tell you, though, that unless patients that
9 fit this profile, that are in this group, understand that
10 the surgeons, the companies who make these devices that
11 these patients desperately need in order to function, will
12 work with us in trying to solve this problem. I don't know
13 that we are ever going to come to a solution with it.

14 And then I would like to use that as a segue into
15 your third question about reimbursement and who is going to
16 pay for this. I think the third leg of that triangle that
17 has to work together on this is our insurance companies. We
18 are talking now about patients who had significant problems
19 that require significant surgical procedures with very
20 technically difficult devices to manufacture and to implant.

21 The insurance industry has to understand that this
22 problem exists, that it is not just a problem that the
23 surgeons have to deal with. It is not just a problem that
24 the patients have to deal with. It is a problem that we all
25 have to deal with.

1 My biggest hope is that somehow we can bring these
2 three groups together and develop an understanding of the
3 problem and the way we can solve it because I think what is
4 going to happen here, the future of this, is the fact that
5 we are going to get over a big curve here and these patients
6 will be able to be treated or managed. I think the better
7 term is managed than treated.

8 And then we are not going to see many of these
9 patients for a period of time. So that is what I hope. I
10 hope that addresses your question.

11 MS. COWLEY: You missed probably the most
12 important component of this picture. You mentioned
13 surgeons, manufacturers and insurance companies. I think
14 you better include the patients in that group, too, to make
15 this change.

16 DR. MERCURI: No; I said the patients.

17 MS. COWLEY: You said three.

18 DR. MERCURI: No; I said the patients, the
19 surgeons and manufacturers and the insurance.

20 MS. COWLEY: Another question on the design
21 failure. I have to comment on this because I understand the
22 trauma a patient goes through just trying to sign a consent
23 form. I just have to find out what you all did for those
24 people who woke up from surgery thinking they were going to
25 have a new TMJ Concepts device and were told they don't have

1 it because the device did not fit, and what did you give
2 them to control outrage?

3 DR. MERCURI: I would like to characterize the
4 reasons that the device didn't fit. All of those cases were
5 my cases, so I can tell you about them. The very first
6 patient that ever was implanted with this device, the device
7 did not fit. And the reason the device did not fit is that
8 Techmedica was an orthopedic company and they felt that the
9 device had to be 8 millimeters thick, the fossa component.

10 An 8 millimeter fossa will not fit into the
11 temporomandibular joint both in a superior-inferior
12 direction and 17-18 millimeters medial-lateral will not fit.
13 Again, it just didn't work. So the patient was awakened and
14 told the device didn't fit. She understood and went--the
15 second one was a patient who moved in the CT scanner. As
16 you saw from the presentation, the model is an extremely
17 important component of this.

18 Two implants did not fit because she moved in the
19 CT scanner. Therefore, of this developed the fact that a
20 graphite rod is now used to assure that if there is movement
21 in the CT scanner that this won't happen again. And that
22 has never happened again.

23 The other one was a patient who--

24 MS. COWLEY: You don't have to go on. It was the
25 emotion of that question.

1 DR. ALTMAN: What sort of training is provided to
2 surgeons on using the TMJ Concepts. The second part of that
3 is how does a patient know that, in fact, the surgeon they
4 are going to has actually been trained, if, in fact, there
5 is training?

6 DR. MERCURI: I would like to be sure I completely
7 understand the question. You are now restricting the
8 question to the TMJ Concepts device and you are no longer
9 talking about Techmedica device.

10 DR. ALTMAN: Correct.

11 DR. MERCURI: Using the PMS study that we are
12 doing now, we have given courses to surgeons and I have
13 personally, in order to be sure that the surgeons know how
14 to put this device and they are putting it in correctly, I
15 have personally gone and proctored surgeons in a number of
16 different places around the United States, obtained
17 privileges to operate with them at surgery, gone into the
18 operating room and actually proctored them placing the
19 devices.

20 DR. ALTMAN: That's great. TMJ Concepts will sell
21 the product to any surgeon that wants to purchase it
22 regardless of whether or not they have received some sort of
23 training? Do you know that?

24 DR. MERCURI: The 510(k) certification allows them
25 to market the device. There are a number of surgeons around

1 the country who are very versed in temporomandibular-joint
2 surgery. There are a number of surgeons around the country
3 who have used what we are calling the Christensen device in
4 the past. It is a very similar installation process in
5 order to place these devices in as the Christensen device.

6 Therefore, not every surgeon needs to be proctored
7 by those surgeons where we know that they have done few
8 temporomandibular-joint reconstructive procedures, those are
9 the ones where I make it a point of going and proctoring.

10 DR. ALTMAN: The second part to that question; how
11 would a patient know whether how to choose--say, they have
12 read about TMJ Concepts and wanted to use that product. How
13 would they find a surgeon who was skilled in using that
14 project?

15 DR. MERCURI: There has been no marketing of this
16 device. This has been a device that has gone by word of
17 mouth. Typically, patients will call TMJ Concepts and speak
18 to either Mr. Sampson or Mr. Rose or other of the engineers,
19 and they will give them the names of the surgeons in their
20 particular area.

21 Or many of the patients will ask, "Who are the
22 surgeons who have performed the most of these surgeries?"
23 and they will be given the names of those surgeons.

24 DR. ALTMAN: Does TMJ Concepts not have--but they
25 do have information to patients on the product and what is

1 to be expected?

2 DR. MERCURI: Yes; there is a brochure, a patient
3 information brochure, that has been developed that talks
4 about what temporomandibular-joint reconstruction involves.
5 It may be part of your--

6 DR. ALTMAN: It was.

7 DR. MERCURI: It is a brochure which I wrote so I
8 know what is in it. It says, "Considering total
9 temporomandibular-joint construction." It talks about the
10 reasons for temporomandibular-joint reconstruction. It
11 talks about what are the causes of the temporomandibular-
12 joint breaking down. It talks about how the surgery is
13 performed, what are some of the possible complications, what
14 can I expect following surgery, how much will my pain be
15 reduced.

16 That is based on the data of 0 to 4, 5 to 9, 10 or
17 more surgeries, how long will this reconstruction last. And
18 we discussed the issue of the orthopedic ten-year business.
19 What can I do to enhance the success of this reconstruction,
20 explaining to them--I think an issue that was brought up was
21 that, in the contraindications, we have talked about the
22 fact that there are patients with continuing aggressive
23 muscular activity.

24 We explain that in here to these patients. That
25 is a surgeon-patient determination as to has a lot of excess

1 muscle activity. Then it goes on to discuss alternatives to
2 temporomandibular-joint reconstruction. Then it goes
3 through the whole--what are the steps involved in the
4 preparation to receive this device. It goes through the
5 whole protocol of how this device is manufactured.

6 And then, what are my responsibilities should I
7 choose to have this device implanted. In those
8 responsibilities are included, "I must see my surgeon for
9 follow-up appointments. I must immediately report to my
10 surgeon any problems. I must take care of my implants. I
11 must request that my implants be returned to TMJ for
12 analysis should they be removed. I must keep TMJ Concepts
13 informed of my current address so that we can follow these
14 patients."

15 When they sign their consent, part of the consent
16 is what I just read. So we are making every possible way of
17 keeping track of these patients.

18 DR. GONZALES: Gilbert Gonzales. I have a
19 clinical question for Dr. Mercuri regarding the visual-
20 analogue scales and the clinical studies measuring pain,
21 function and diet. When I looked through the paperwork that
22 was given to us, and the studies, the data collection was
23 stated to be in a standardized manner.

24 It seems that, in the first study and second
25 study, pain and opening, that the numbers of patients

1 throughout 2 through 72 months varied. If the data
2 collection was in a standardized fashion where I am
3 supposing, and the question is really how this was
4 standardized; that is to say, the visual-analogue scale was
5 given before and after surgery at set times.

6 Pain is rarely a constant phenomenon. Oftentimes,
7 especially in TMJ patients and others, you will have an
8 incident component, a component that occurs with activity
9 following eating, with joint positioning, sleeping, other
10 points, where you will have worsening of the pain or you
11 will have a constant pain with intermittent incident pain.

12 So the point that you measure pain becomes very
13 critical. When you ask a patient, for instance, what their
14 pain level was immediately after eating, for instance, it
15 may be very different than asking them when they have been
16 sitting in an office or waiting room or when they awaken in
17 the morning or other times.

18 So my question, first, revolves around when these
19 patients were asked about their pain. Was it when they came
20 in for their visits and, if it was when they came in for
21 their visits, I don't understand why, in some cases, pain
22 was measured and opening was not in some patients, if you
23 look at the groups of patients, and, in other cases, opening
24 was measured in some patients and pain was not.

25 If this was standardized where this standard form

1 is asking both pain and opening questions, why is it that
2 patients didn't either fill it out, or only filled out part
3 of it? . Were some of the questionnaires or the standardized
4 form mailed to patients and then mailed back?

5 I guess the first part of the question is when
6 were the patients asked to fill out the form and then the
7 second part is why is it that there was variability in only
8 part of the form being filled out, apparently from--at least
9 I am extrapolating that from the difference in the numbers?

10 Finally, the third part of that question is the
11 intermittent nature aspect of pain, the incident pain that
12 occurs, apparently was not taken into consideration, or was
13 it, in a manner that you had them fill out the visual-
14 analogues scales?

15 DR. MERCURI: Let me start out by saying the
16 optimum word here, or the word we are talking about, is
17 standardized. The form was standardized so it is a standard
18 form. The form was administered to patients preoperatively,
19 obviously before they had their surgery, and then at each
20 follow-up appointment. The patients were told that when
21 they make their mark, the mark should not be at the worst
22 possible pain that they have, as you have characterized,
23 during function, but generally, where is your pain level,
24 generally, during the day.

25 In order to characterize the pain the way you have

1 talked about it, we would have to take a visual-analogue
2 scale more like a global-pain questionnaire. We would have
3 to say, "At 2 o'clock, what was your pain? At 3 o'clock,
4 what was your pain? At 4 o'clock?" which is an onerous kind
5 of thing for people to do.

6 Having been in pain research, I know that some of
7 those patients will do that and many patients won't. So,
8 for this particular study, again, because we are dealing
9 with so many different types of surgeries, we wanted to make
10 it as simple as possible.

11 So we said, "What is your pain level generally;
12 not when you function?" Where we got at the function part
13 of this, because we realized, just as you just stated, that
14 there are variabilities, "Where is your function level? How
15 well do you function?" "I cannot function," or, "I can
16 function as much as I want on my diet." So that is where we
17 got at the variabilities related to function and chewing.

18 The third component of your question was--

19 DR. GONZALES: The study 1 and study 2, you have
20 patients at various months where the numbers vary where some
21 patients apparently filled out the pain questionnaire part
22 and some did not fill out the opening part. It just doesn't
23 fit.

24 DR. MERCURI: There are two reasons for that, at
25 least two reasons for that. One is, again, the fact that

1 some of these patients were evaluated by the dentist,
2 physician, surgeon who sent the patient to the surgeon who
3 implanted the device at a distant site and just didn't
4 complete the form.

5 Another was that some of the patients were
6 evaluated by office staff rather than the surgeon who did
7 the procedure and just didn't complete the form. The third
8 reason is that in order to--and this was my particular
9 patients--in order to get data from patients who were out of
10 state that refused to come back, I made up a questionnaire
11 and included a measuring device with instructions on how to
12 measure it.

13 The patients would fill that form out and send it
14 back to me. Some of the patients didn't understand the
15 instructions. Some of the patients didn't send the forms
16 back. Some of them sent them back not filled out.

17 Taking all that into consideration, do we throw
18 out all of that data when it wasn't completely filled out or
19 do we put the data in and pool the data as we have done at
20 the various points, the more data the better kind of thing?
21 So that is how it happens.

22 DR. GONZALES: My concern in this is that the
23 statistics are as good as the basic units of information. I
24 am just a little concerned about this point of measurement
25 knowing that pain is incredibly variable. You can ask the

1 patient, for instance, to fill it out at one point or at
2 another point and get discrepancies in the measurement.

3 So standardization is very, very important when
4 you are talking about pain because if you ask a patient what
5 their worst pain is, it is notorious that the memory of pain
6 is not very good. People do not have a good memory of pain.
7 The visual-analogue scales were created for on the spot, at
8 that moment, what your pain level is not what it was in the
9 previous twenty-four hours.

10 So that is one of my concerns about the data is it
11 is based on this information that could have that
12 variability in it; that is to say, of the pain fluctuation.

13 DR. MERCURI: All of the patients were given the
14 same instructions so they all gave the report of pain the
15 same way at each time interval.

16 DR. GONZALES: And those instructions were written
17 out instructions that every patient received?

18 DR. MERCURI: No; they were not written
19 instructions.

20 DR. GONZALES: Those were verbal instructions.

21 DR. MERCURI: Verbal instructions.

22 DR. GONZALES: That were given by you, by the
23 nurse, by office members, so it really wasn't standardized,
24 then.

25 DR. MERCURI: No; I said initially that the form

1 was the standard part of this but each one of the datapoints
2 was based on the same definition of what pain was, the same
3 definition of pain, where your pain generally is.

4 DR. GONZALES: Another question regarding the ten
5 or greater surgical--I will call them surgical patients,
6 patients who have had ten or more surgical procedures. Your
7 charts show that the patients don't get better over time in
8 terms of their pain. Certainly, with your function
9 measurements, they got better.

10 You do include a precaution in one of your--I
11 guess this is a handout to patients where you state, "Total
12 TMJ replacement should be undertaken with extreme caution in
13 patients who have undergone ten or more surgeries. Pain-
14 management team consultation should probably be mandatory."

15 Is that now the case that the patients that come
16 to you--and is that something that you are instructing other
17 physicians--certainly, with patients who undergo, for
18 instance, spinal-cord stimulators or any pain procedures, we
19 find that it is mandatory that those patients be evaluated
20 by a multidisciplinary pain clinic and, certainly, a pain
21 psychologist not because, necessarily, we feel that the
22 patient has premorbid psychological problems but because
23 patients who suffer with pain for such a prolonged period of
24 time, everyone will develop psychological problems,
25 depression, anxiety, on and on and on.

1 So it would seem to me that, based on what you
2 have already noted and are instructions to patients and,
3 apparently, physicians as well, that any patient with ten
4 surgeries or more procedures like that should be mandatorily
5 directed to a multidisciplinary pain clinic and pain
6 psychologist to be able to evaluate them further as a
7 protection for them, because these patients, also, have a
8 much higher risk of suicide and other pathology that occurs
9 to them psychologically.

10 The question is what have you learned from doing
11 this in terms of these patients? Are you instructing
12 physicians, or is it part of the plan to have patients be
13 directed to multidisciplinary pain clinics?

14 DR. MERCURI: Someone asked a similar question
15 before and I addressed it by saying--I wasn't specific for
16 the ten patients or more but I think the question was do you
17 send any of these patients for psychological evaluation.
18 Most of the patients, I would say the vast majority of the
19 patients, that have had ten or more operations are already
20 in a pain-clinic environment.

21 If they are not in a pain-clinic environment, they
22 get to a pain-clinic environment. So I think that issue has
23 already been addressed.

24 The problematic patients, though, are the ones
25 that fall in the 5 to 9 category. As I mentioned earlier, a

1 lot of those patients have been so frustrated by their walk
2 down the TMJ path that, as soon as you start mentioning, "I
3 think it is important that you see a psychologist or a
4 psychiatrist or go through our pain clinic," many of those
5 patients turn around and walk out the door.

6 I don't think we should be scaring patients away.
7 I agree with you because, as I stated before, I have done
8 pain research. I know what chronic pain does to patients
9 and the psychological component to it. But, right now,
10 there is no protocol for that group of patients.

11 But, to address your specific question about the
12 ten or more operations, the vast majority, if not all, of
13 those patients are already in that environment.

14 DR. JANOSKY: At this time, I would like to take a
15 fifteen minute break returning at 4:10. We will continue
16 with some more open committee discussion.

17 [Break.]

18 DR. JANOSKY: I would like to continue with the
19 open committee discussion with questions from Dr. patters.

20 DR. PATTERS: To me, the overriding issue here is
21 whether the subset of 66 patients, where, in my mind, the
22 statistical data suggests clear efficacy or clear
23 effectiveness and safety of the implant, whether that
24 actually reflects the total patient experience.

25 So I have a question to Dr. Mercuri, if I could,

1 and then to Ms. Cowley or other members of the TMJ
2 Association.

3 Dr. Mercuri, if I understand correctly, these data
4 were not gathered prospectively in a research protocol but
5 rather as part of clinical practice; is that correct?

6 DR. MERCURI: According to the 1995 paper, these
7 data were collected prospectively. In other words, the
8 inclusion and exclusion criteria were proposed in the paper.
9 The indications were proposed in the paper and the protocol
10 was proposed in the paper.

11 DR. PATTERS: But the patients paid for their
12 treatment and you said that they paid for follow-up visits
13 after 90 days. So the company did not support this care.

14 DR. MERCURI: That's correct. It was a limited
15 clinical trial.

16 DR. PATTERS: Did these patients know they were in
17 a research protocol?

18 DR. MERCURI: Yes.

19 DR. PATTERS: And they consented to that.

20 DR. MERCURI: Yes.

21 DR. PATTERS: And they consented to the follow-up
22 visits that would be required? They were specified up-
23 front?

24 DR. MERCURI: They were specified up-front as they
25 are now in the PMS.

1 DR. PATTERS: And there was a fee to those
2 patients for those follow-up visits after 90 days?

3 DR. MERCURI: I can only tell you about my own
4 practice. To this date, if a patient shows up ten-years
5 postoperatively, there is no fee. I cannot address the
6 other participants.

7 DR. PATTERS: But it is possible that that had
8 something to do with the loss of patients to follow up from
9 other practices.

10 DR. MERCURI: It is possible.

11 DR. PATTERS: Ms. Cowley, I need to understand
12 from you who has a probably a very good understanding of how
13 these patients might feel and think, when patients do not
14 return for follow up, do you believe that that is a subset
15 of patients that are dissatisfied, a subset of patients that
16 are extremely happy, or is that just a random event and it
17 doesn't bias those who return.

18 MS. COWLEY: I have not heard from anybody
19 ecstatic over much of any TMJ treatment. In other words, no
20 one has called to say, "This is the best thing that has
21 happened to me."

22 Certainly, we have patients who have called and
23 said, "Yes; I am improved." Unfortunately, we are now
24 hearing from them eight years later and a lot of other
25 problems have set in.

1 My gut instinct tells me that so many of the TMJ
2 patients have been there, done that, paid thousands,
3 hundreds of thousands of dollars, for treatment. The
4 disillusionment with, perhaps, in a case like not a failed
5 device but the problems associated with the disease and the
6 device and where they are at that point may be very--they
7 just throw up their hands in despair.

8 DR. PATTERS: But the data from 66 patients
9 clearly shows, in my mind, that these 66 patients got
10 better. So I am trying to find out about the other 150. I
11 want to know, in your mind, since they did not return for
12 all their follow-up visits, if you think that those were
13 patients who were likely didn't get better, got much better
14 and didn't feel the need to come back, or it is just a
15 random chance and the 66 reflects those also.

16 Perhaps you can't answer that, but you certainly
17 know the patients better than I would.

18 MS. COWLEY: I think it would be unfair. I can
19 tell you what I hear from patients. Usually the problems
20 set in and they don't want to go back to the doctor. They
21 are looking for another one. But, on the other hand, many
22 patients in the last three years are tending to not seek any
23 treatment whatsoever. They are trying to just stay where
24 they are because one more surgery equals more pain, and on
25 and on.

1 So they may be this much better but not great. I
2 wish we had data.

3 DR. PATTERS: Then I will ask you, personally. Do
4 you think the experience of the 66 that are presented--do
5 you think that is the representative experience of this
6 device or do you think that 150 have a whole other story to
7 tell?

8 MS. COWLEY: That is a tremendous responsibility
9 upon me. I would absolutely in no way want to be unfair to
10 any manufacturer.

11 DR. PATTERS: Then I will ask, perhaps, the
12 representatives of TMJ Association who is not sitting at the
13 table if they have any comments.

14 DR. ZUCKERMAN: If you don't mind my responding
15 for the National Women's Health Network. I am Diana
16 Zuckerman. Prior to my working in Congress, I was a project
17 director and university faculty member at Harvard and Yale
18 and did research all the time. I would certainly say that
19 my experience was that people drop out for a variety of
20 reasons, but in a case like this when people are in pain,
21 certainly, I don't think that is the time they fill out
22 their questionnaires.

23 That worried me that people weren't necessarily
24 coming in for exams but filling out questionnaires at home.

25 When I did follow up--it is always difficult to

1 get people to stay in a study. Usually, you have to provide
2 incentives for them to stay in a study. Certainly, it is
3 the opposite of an incentive to tell people, "Well, come on
4 in but you will have to pay to participate in this study."

5 People who are happy, people feeling better, might
6 be willing to do that because they are so grateful. People
7 who are not doing so well, it seems to me, would be the
8 least likely to come in and pay for the experience of
9 telling a doctor, who didn't help them, how badly they feel.

10 To me, as a researcher, that is just common sense.
11 Also I just wanted to mention what seemed to me an inherent
12 bias in when the pain was measured. Prior to surgery, it
13 seems to me, is when you feel the worst. When things are
14 really bad and the pain is so bad you can't stand it
15 anymore, that is when you go in for surgery. You've had it
16 and you will try anything.

17 It seems to me that you come in for your follow-up
18 visits or you fill out a questionnaire in your home when you
19 are feeling a little bit better. When you are writhing in
20 pain at home isn't when you say, "Oh; I have a questionnaire
21 to fill out. I think I'll do that now."

22 It just doesn't work that way. So that concerned
23 me, that there was that bias, that people weren't coming at
24 regular times with an incentive to come in and objectively
25 be evaluated as to how they feel.

1 In most studies, of course, people usually
2 participate when they are feeling really strongly either
3 positively or negatively, and that is always a bias. But,
4 in this particular case, when you are dealing with people
5 with so much pain, and maybe Terry Cowley can address this,
6 but when you are in a lot of pain, it seems to me, that is
7 not when you want to participate in a study, usually.

8 DR. ALTMAN: Can I respond to that as well? I
9 think my experience in fifteen years of public health and
10 doing an awful lot of surveys is just the opposite of that
11 and that people that are the unhappiest are the ones that
12 you do hear from. The people that are happy are the people
13 that tend to not answer things because things are okay.

14 I think what we have heard from the TMJ
15 Association earlier is, in fact, that people that they hear
16 from are the folks that are having some problems. They
17 don't have a whole big data--they didn't give us examples of
18 people that were happy, but people that are not.

19 My experience is that people that are not happy
20 with the system are the ones that you hear from.

21 MS. COWLEY: I think when you have choices of
22 professional providers, it is much easier for you to call
23 the person up who you are not happy with and tell them, "I
24 don't appreciate what just happened," or, "I am just not
25 better."

1 The TMJ patients, over the last ten years, have
2 had their professional sources limited severely. They are
3 far more limited if you do not have money to travel across
4 the country for treatment which means, if you only have
5 three oral surgeons in your community, you kind of are
6 married to Dr. Love because no one else will see you.

7 There is sort of what I would explain as a little
8 emotional blackmail going on where you have got to, as
9 patients will tell us--"We have to tell him what he wants to
10 hear. We can't appear to know too much because then he asks
11 me if I want to treat myself and get out."

12 So there is this intimidation factor involved. If
13 you happen to find another doctor and that doctor happens to
14 dump you, abandon you, then you might have to go back to Dr.
15 No. 7. We don't have an awful lot of open communication
16 about this.

17 Why, perhaps, nobody trusts anybody anymore, will
18 not fill out the FDA MedWatch forms, will not complain about
19 their device failure to anyone except us, sort of in an
20 underground manner.

21 It would be wonderful if all of these people that
22 weren't in the numbers were out there having a life. Heaven
23 knows, we would like to believe that. We want proof, in a
24 way.

25 DR. PATTERS: I am looking for scientifically

1 valid data in a relatively complex situation with a very
2 complex patient in a very complex protocol with lots of
3 holes in it. So I am trying to look at it as objectively as
4 possible to ask, "You proved it for 66 selected patients.
5 Is it true for the other 150?" I guess we don't know.

6 DR. LI: First of all, a follow-up to Dr. Burton's
7 question about comparison to orthopedic devices just as a
8 benchmark. Recognizing, of course, that the patient
9 populations are completely different and the longer history
10 of the total joints, and depending on which statistics are
11 used, in one set, it has been proposed that the failure was
12 8 percent in the first 300-and-so-odd, if you count them a
13 certain way.

14 Under those conditions, those would have been an
15 alarmingly high failure rate. Typical for the state of the
16 art to where we call a gold-standard total hip or total
17 knee, the survivorship is around 95 percent at fifteen
18 years. Usually, the first five years, anything above about
19 a 1 to 1.5 percent failure, which are almost exclusively
20 infection, are considered to be too high.

21 But, again, that is a completely different patient
22 set and experience.

23 A follow-up question to Dr. Mercuri. Did you do
24 any kind of clinical wear assessment? I saw some very nice
25 looking radiographs there that appeared, for one who spends

1 a lot of time measuring hip and knee wear, would lend itself
2 to radiograph analysis of at least head penetration.

3 So did you do that on any of your patients,
4 especially when you get out to six, seven years?

5 DR. MERCURI: As we talked about, and as Mr. Rose
6 presented and the FDA presented, the amount of wear is so
7 small and the imaging that we using is gross, that we can't
8 really measure wear on these particular images for the
9 factor that, number one, it is so small, and, number two, we
10 don't have a standardized way of doing it.

11 Now, I realize that there are cephalometric
12 radiographs that can be done to measure wear but, again,
13 because the wear is so small, I don't think we can do that.

14 DR. LI: But your notion that the wear is small
15 comes from the laboratory data; is that correct?

16 DR. MERCURI: That's correct.

17 DR. LI: So if, for instance, the laboratory data
18 was not a true reflection of the in vivo situation, then
19 that assumption may or may not be true. So it is somewhat
20 surprising, I guess, given the fact that the loads are as
21 high as the applicant has specified they are through the
22 finite-element model and the fact that you have, perhaps,
23 down to a 3-millimeter thick piece of polyethylene and that
24 you have got non-zero wear in the hip simulation that you
25 would see no wear in the clinic.

1 Actually, as I punched through the numbers at
2 seven and eight years, it should be relatively evident. If
3 you take, for instance, the highest wear in your wear test,
4 laboratory test, that would be quite evident in a normal-
5 quality X-ray.

6 DR. MERCURI: Again, looking at the clinical data,
7 and I will let Mr. Rose address the engineering data, we are
8 not seeing failures.

9 DR. LI: Understood. But you are not looking for
10 wear, either, apparently, though, I guess is my question.

11 DR. MERCURI: Wear would show itself up as
12 inflammatory response.

13 DR. LI: Well before that, you ought to--well, let
14 me take the example of total hips and knees again. Well
15 before you get an inflammatory response, you can see, for
16 instance, the relative migration of the metal component
17 relative to the polyethylene, especially in this case where
18 you have polyethylene with the metal back, it gives you a
19 nice radiographic marker for the back of the polyethylene,
20 would lend itself to that marker.

21 The other signs of wear, of course, are any kind
22 of loss of radiodensity in the bone. Well before
23 osteolysis, the bone begins to fade. The other portion, and
24 I will sneak another question in in this regard, is that one
25 of the consequences of osteolysis is loosening of the

1 implant which causes pain.

2 So a question I had for you, and I am not sure you
3 can answer this, but when a patient, several years out,
4 after getting one of these devices, records some level of
5 pain on your scale, how do you know that pain isn't from
6 actually the implant being loose as opposed to the pain they
7 experienced when they first came in to you?

8 DR. MERCURI: Let me address the issue of the
9 migration of the implant. We make radiographs at each one
10 of the datapoints to look at the relative position, in using
11 a cephalometric radiograph, anterior-posterior cephalometric
12 radiograph, on the same machine, we can overlay the previous
13 cephalometric radiograph, let's say from two years to three
14 years to four years.

15 So that is kind of a gross mechanism of measuring
16 whether the implant has changed.

17 The second question you had was how do we know
18 that it is not loose. My experience is not with orthopedic
19 hips and knees but with temporomandibular-joint implants is
20 that when a screw is loose or a component is loose, the
21 first complaint that the patient brings to us is not just
22 pain but also swelling.

23 You have to understand that these devices lie very
24 close to the skin as opposed to a hip which is buried in a
25 lot of muscle and so any looseness of screws or any

1 looseness of components will manifest itself as an
2 inflammatory response and swelling.

3 I presented a PMMA-mantled device for the fossa.
4 I don't have the radiographs here with me but the way that
5 was manifested was not that I could see the crack in the
6 PMMA but the fact that the screws that held it to the
7 zygomatic arch were loose and with radiolucencies, and that
8 the fossa underneath the implant was radiolucent.

9 DR. LI: Was it possible that pain--and, again, I
10 am drawing on my hip and knee background so this may not
11 hold true so let me ask it as a question, for total hips and
12 total knees, the type of loosening that I am referring to
13 usually cannot be seen by the eye. It is usually in the
14 order of microns, so it certainly would be invisible to the
15 X-ray and certainly would not manifest itself from any
16 movement of the screw.

17 So well before you actually get a macroscopic
18 visualization, the implant becomes loose enough, and bone
19 doesn't like to be rubbed against, even on the order of
20 microns, and that causes pain. So that is really what I
21 mean by loose, not so much a gross loosening but how do you
22 know these implants are not, on some very micron scale,
23 loose and are causing the pain?

24 DR. MERCURI: I can't tell you that.

25 DR. LI: Let me ask the company a question, then.

1 Have you done micro-motion studies in the laboratory where
2 you fix your device in cadaver mandibles and then try to do
3 micro-motion studies to actually see the amount of
4 micromotion as a function of screw placement and the number
5 of screws or the size of the screws or the shape of the
6 device?

7 MR. ROSE: No; we have not.

8 I wanted to address your earlier question, Dr. Li,
9 on the penetrative wear ability, to use radiographs.
10 Because of the custom nature of these prostheses, the mesh
11 backing to the fossa component is completely irregular and
12 is actually formed to the patient as opposed to orthopedics
13 where there is usually a flat metal plate on a tibial
14 component of some other form of regular geometry which you
15 can assess if you have got migration of two components close
16 to each other.

17 It is very difficult in this device to come up
18 with any of that because of the irregular nature of this
19 back. Also, if the patient slightly changes their position
20 in which the radiograph is taken, it further complicates
21 that.

22 DR. LI: One final question. How sensitive is
23 your device to placement and alignment. For instance, in
24 the wear test, I presume you are well aligned in your device
25 where the condyle is basically articulated where you would

1 like it to on the polyethylene.

2 In surgery, maybe for someone less skilled than
3 Dr. Mercuri, how tough is it to actually get this thing into
4 what you would call an appropriate alignment and what are
5 the consequences if you are out of alignment.

6 I guess this would be at any plan, either A/P,
7 medial-lateral, or even if there is a tilt especially to the
8 polyethylene because the stresses, if you get out to the
9 edge of the polyethylene can be enormous if you are out of
10 alignment on such a small component.

11 DR. MERCURI: That's correct. That is one of the
12 advantages of a patient-fitted device. At surgery, the
13 model, which I hope you have taken advantage of looking at,
14 is available. When I do the surgery, as I discussed at Dr.
15 Altman's question, monitor or proctor the surgery, the
16 design is drawn on the model.

17 The surgeon has the model at surgery. There are
18 various landmarks. From my presentation, you may have seen
19 that the anatomy is so different than the normal anatomy
20 that it is almost, in many cases, like a lock and key
21 mechanism, that this implant will only fit in one particular
22 plane of space.

23 Also, the instrumentation that has been developed
24 for placement of the implant assures that once the implant
25 is placed technically, at surgery, that it is seated in the

1 proper position so that there are no rocking motions to it.
2 So the patient-fit component of it is one. Two, the
3 instrumentation.

4 The third thing is the fact that when these
5 devices are placed in a patient, the patient's occlusion has
6 been predetermined and the patient's jaws are wired together
7 so that immediately you will know if this thing is not in
8 the proper position because you will be able to see that the
9 patient--it won't fit.

10 And then you have to go back, be assured that you
11 are in the proper occlusion, and you have to place it to its
12 home position based on the occlusion.

13 So, for those three factors, it is unusual--rare--
14 that these devices, with this particular implant system, do
15 not fit.

16 DR. JANOSKY: One final question for Dr. Heffez
17 and then we will move to the open public hearing.

18 DR. HEFFEZ: Could I have some idea of the
19 breakdown of the indications for intervention between
20 correction of iatrogenic disease versus non-iatrogenic
21 disease? How many patients were treated in order to correct
22 a problem that was created by, for example, a
23 Proplast/Teflon or Vitek implant?

24 DR. MERCURI: If you would just give me one second
25 to--

1 DR. HEFFEZ: While you are working on that
2 question, if I could ask Mr. Rose, what is the CT scan that
3 is obtained to generate that model? What is the thickness
4 of the scan that is used in order to reconstruct that image?

5 MR. ROSE: The area of interest, near the fossa
6 geometry, I believe we are using 1-millimeter slices on the
7 scan. As we proceed down through the mandible, depending on
8 the type of scanner that is used, that is opened up
9 slightly.

10 DR. MERCURI: In response to Dr. Heffez' question,
11 I would like to refer the panel back to the failure data
12 that was reported on these 162 patients based on study 1 and
13 study 2. We can see here, these are the patients with
14 failed surgery, either grafts or devices. It will kind of
15 give you an idea of the percentage of patients that are in
16 each one of these categories.

17 I think this is the best characterization that I
18 can give you.

19 DR. HEFFEZ: But those 162 patients, were they
20 operated with this TMJ Concepts?

21 DR. MERCURI: Yes.

22 DR. HEFFEZ: They were operated because of those
23 reasons?

24 DR. MERCURI: For these reasons; right.

25 DR. HEFFEZ: Have you broken out your data

1 according to each of those? Let me backtrack. You're
2 classifying it as failed devices, failed grafts. I would
3 like to know how many were treated for inflammatory disease,
4 for example, or traumatic disease?

5 DR. MERCURI: How many rheumatoid arthritis?

6 DR. HEFFEZ: Yes; as opposed to how many of those
7 are--many of those are iatrogenic problems, basically.

8 DR. MERCURI: Yes.

9 DR. HEFFEZ: I want to know how many were virgin
10 joints and how many were inflammatory disease, tumor. What
11 is that subset?

12 DR. MERCURI: I don't have that data with me.
13 This is the best I can give you to characterize that. I
14 would be happy to provide that to you. I have that data. I
15 just don't have it with me.

16 DR. STEPHENS: One question on that graph, does
17 the failed graft group represent grafts that been done for
18 Vittek implants that had failed? On other words, are there
19 some failed Vitteks in that failed graft group?

20 DR. MERCURI: Yes.

21 DR. BURTON: One other question which goes off
22 that graph as well. This 162 patients, can you give us at
23 least a somewhat demographic breakdown of when they were
24 done in terms of how many were done three to five years ago
25 and how many have been done one year ago, two years ago,

1 three years ago?

2 MR. ROSE: This is actually the data from our
3 active postmarket surveillance study, so these 162 patients
4 have been done since December of '97.

5 DR. BURTON: Thank you.

6 DR. JANOSKY: At this time, we would like to open
7 the public hearing again.

8 **Open Public Hearing**

9 DR. JANOSKY: I would ask that anyone who wishes
10 to speak state their name, their affiliation, any current or
11 previous interests, financial interests. Can I see by a
12 show of hands if there are.

13 It looks like the list from this morning, if I am
14 correct. Do you want to do the same order from this
15 morning? Each of you will be given three minutes to address
16 the panel. We will start with Ms. Lisa Brown from TMJ
17 Association.

18 MS. BROWN: I will be real brief. A lot of
19 people, after five to nine surgeries, these surgeries could
20 range anywhere from \$3,000, \$30,000-plus, each. They run
21 out of money. Although they would really like to go and
22 have the follow ups, they don't have the money to do it.
23 Insurance companies as well, they will cover three to four
24 follow ups and then, after that, these people are no longer
25 covered.

1 Three to four follow ups, I don't know that that
2 would constitute a year of follow up for someone. I think
3 there is more than I would like to say--a number of people
4 out there that fall into this category that cannot afford
5 it. They are on disability, social security. They would
6 love to have the follow up but they can't afford to get
7 there.

8 I gave a few examples this morning of that very
9 thing from comments from people saying that they couldn't
10 afford it and they didn't know what to do.

11 That's all.

12 DR. JANOSKY: Thank you.

13 Next is Mr. Kevin Clark from TMJ Association.

14 MR. CLARK: Kevin Clark with the TMJ Association.
15 I would like to follow up, I guess, what Dr. Patters, your
16 questions to Terry and anybody in the TMJ Association with
17 respect to the science behind this particular study.

18 I don't think we are in a position to validate or
19 invalidate the science that you have heard about today. I
20 think that is the panel's job to do so. But I would take
21 exception to something that you mentioned over here. In any
22 business, an unhappy customer is more likely to complain
23 something like ten times. You hear ten times over the
24 negative, versus the happy customer that walks away and
25 says, "That is a great product."

1 With respect to the TMJ patients who have been
2 hurt or wronged or whatever you want to phrase it, I don't
3 think they typically go back to their surgeon to complain.
4 Sometimes they do, but maybe they get a kind of a, "Maybe it
5 is possibly your fault," or, "It is in your head. It will
6 get better," whatever answers they hear.

7 But typically, and I have been through this for
8 thirteen years with my wife who has had six surgeries and
9 five of those were bilateral. She has two different types
10 of implants right now. I have to admit that for the first
11 several years, we were very intimidated to go back to
12 complain to the surgeon. We didn't know quite what to do.

13 Since then, we have gotten close to some surgeons
14 and hooking up with the TMJ Association and really taking
15 matters into my own hands and getting into this to
16 understand it better has made me more confident to be able
17 to ask the questions that we need to ask.

18 But that is not your average patient. Your
19 average patient is paranoid, extremely intimidated, of their
20 surgeon. So I am not sure those are the ones that are
21 coming back to follow up. So I just wanted to throw that
22 in.

23 Lastly, Dr. Patters, you asked what we would like
24 to see from the Association, or maybe even personally. I
25 think it is the panel's job to decide whether the science is

1 there for any of these implants being presented this week.
2 But, personally, obviously, as I mentioned earlier, my wife
3 has got two different types of implants and they appear to
4 be failing.

5 We do need something if they are failing. If
6 speak for her. I speak for thousands of other patients that
7 I believe that are out there that are in the same
8 predicament. I don't know what the answer is. Would we
9 like to see approval of one of these two products? That is
10 up to the panel to decide. I would like to see approval at
11 some point at some time of something that is going to help
12 my wife out and the other patients across the country.

13 I don't know what shape or form that comes in and
14 I don't know the FDA process real well, but I understand
15 there is conditional approval, there are conditional
16 approvals for certain indications and maybe some combination
17 thereof is the answer. Again, that is up to the panel.

18 Obviously, if you approve a device for certain
19 indications, that device, once approved, as I understand it,
20 can be used kind of as a blanket device. It is approved for
21 this indication or that indication but anybody can implant
22 it for other indications that it is not approved for, as I
23 understand it again. I am not an FDA person.

24 With that, maybe I can ask the company just one
25 question. In the case of virgin joints, at what point--and

1 maybe Dr. Mercuri, as a practicing clinician can answer this
2 best, what do you need to see before a device is put in?
3 How bad off, if you will, does a patient have to be?

4 Thank you.

5 DR. MERCURI: Unfortunately, that is a very
6 difficult question to answer because all patients are
7 completely different. What may be an indication for one
8 patient may be a contraindication for another patient. When
9 we look at the indications that I discussed earlier, I think
10 those are solid indications for placement of a patient-
11 fitted temporomandibular-joint device such as the TMJ
12 Concepts device.

13 But I can't tell you, as I sit here today, without
14 having a specific patient in front of me--and that is why I
15 find this particular device to be the most useful because it
16 is patient-specific for the specific patient and the
17 specific problem that that patient has. So I am hoping that
18 that answer will satisfy you.

19 DR. HEFFEZ: Those indications that you listed,
20 which ones of those are imperative, in your mind, that this
21 device would be required, that there would be not another
22 alternative method of reconstructing that joint if
23 indicated?

24 DR. MERCURI: I believe all of them are.

25 DR. HEFFEZ: So you feel that there is no other

1 viable means of reconstructing the temporomandibular joint
2 in those indications listed besides using this device.

3 DR. MERCURI: I would like you to remember my
4 characterization of these patients. These are multiply
5 operated, anatomically mutilated, patients or
6 physiologically mutilated patients such as a rheumatoid
7 patient, or an ankylosis patient.

8 I believe on the basis of principles of orthopedic
9 joint placement that these devices must be stable in situ
10 and they must be made for the specific indication, the
11 specific problem, that is there. Right now, in my clinical
12 experience, the only device that I feel comfortable with, as
13 a clinician, in placing is a specific device such as the TMJ
14 Concepts device.

15 DR. HEFFEZ: I am not necessarily talking about
16 the device. I am saying there is no other alternative means
17 of reconstructing the temporomandibular joint besides using
18 this device on those indications that you listed.

19 DR. MERCURI: There are other ways to reconstruct
20 the temporomandibular joint using autogenous tissues.

21 DR. HEFFEZ: Right. So which one is imperative,
22 in your mind, that even autogenous material wouldn't be
23 indicated and that you would have to use this device.

24 DR. MERCURI: As I said, I think for the patient
25 population that I characterized, it is this device. If you

1 are going to talk about ankylosis, primary ankylosis, in a
2 child, this device is not a reasonable device to place in a
3 child.

4 DR. HEFFEZ: Yes, but you didn't list that in your
5 indications.

6 DR. MERCURI: No. It is one of the
7 contraindications.

8 DR. HEFFEZ: I am saying in the indications, as
9 ankylosis, or the indication is rheumatoid arthritic, is the
10 only way of reconstructing that individual using this
11 device, in your mind, or there are other alternative means?
12 I want to try to identify if there is a specific indication
13 in your mind where there currently is no alternative
14 reconstructive method.

15 DR. MERCURI: Certainly the patient who has had,
16 because of the data that was presented in the Wolford and
17 Cottrell paper, it appears that an alloplastic device such
18 as the TMJ Concepts device is the only device that can deal
19 with that situation. That is certainly one of the absolute
20 indications, but I have to stand by what I said before that
21 I believe that this device is the device for reconstruction
22 of the patients the way I have characterized them.

23 DR. HEFFEZ: The Wolford paper was regarding the
24 Proplast/Teflon implants.

25 DR. MERCURI: Yes.

1 DR. JANOSKY: Dr. Diana Zuckerman from the
2 National Women's Health Network.

3 DR. ZUCKERMAN: Thank you. I actually have a
4 question for Terry Cowley. She said something and I want to
5 make sure I understand it correctly. It was my
6 understanding that what you said in the follow-up study
7 where there are only two doctors taking patients that one of
8 them--that you know of at least one patient who said he
9 wouldn't see her for follow up because she owed him money.

10 So the concern was that if patients owed--out of
11 only two doctors in the study that if patients owed one of
12 them money, they couldn't come back for follow up. So it
13 wasn't just that they had to pay to see the person but also,
14 if they owed money, they couldn't come; is that correct?

15 MS. COWLEY: If they had a balance on the account.

16 DR. ZUCKERMAN: Balance due.

17 MS. COWLEY: Yes. The staff sort of kept the
18 patient out. We did hear that quite a few times.

19 DR. ZUCKERMAN: I guess my concern is, as a
20 researcher--I mean, this is just against everything that you
21 do. In research, you try to get as many people in for
22 follow up as possible. You don't create barriers to them
23 coming back in. I guess that is why there are only three
24 people at the end of some of these studies, or six.

25 You don't know, as you pointed out, whether that

1 is a random three or a random six, or whether the people who
2 owe money are the worst off or not.

3 MS. COWLEY: Have I answered your question?

4 DR. ZUCKERMAN: Yes.

5 MS. COWLEY: Am I able to follow up on that? I
6 think this brings into discussion one of the--another can of
7 worms of all of this TMJ mess and that is patients will call
8 us with complaints. We have to keep their patient
9 confidentiality. Many times, I ask, can I tell the FDA
10 about this? They say, "Absolutely not because they will
11 know I am the patient with the device implanted sideways,"
12 or whatever.

13 So I think one thing that we desperately lack is a
14 network where we can communicate openly, honestly, where the
15 patients are not living with this emotional blackmail if
16 they complain to the FDA they are going to be marked, their
17 surgeon will never see them again.

18 We have to be able to communicate openly with the
19 manufacturers. My ideal situation would be where we have
20 one implant registry, period, for all TMJ devices. I would
21 like to see all the devices sent to one central location
22 where they are sent to the hospital only for that patient
23 because I hear of patients waking up with a device they
24 didn't know they were getting.

25 We somehow have got to clean this system up and we

1 have to be able to work with the good manufacturers. We
2 have to get some funding from the FDA, from the NIH, to set
3 up some type of registry, some type of studies.

4 The gentleman over there said it is imperative we
5 have pain control and go to pain clinics. I would like to
6 know why we have a medical doctor who doesn't understand
7 anything about temporomandibular-joint diseases, disorders,
8 as well as particle disease so many of these patients are
9 suffering from.

10 We routinely hear now of vision damage where
11 particles are in the eye, they are migrating. We hear of
12 seizures. This is constant. If you ask a patient, "Can you
13 open your mouth?" "Yeah, but I am seizing every day."

14 We need a network of medical people, dental
15 people, manufacturers that can start putting together a
16 picture of what is this TMJ patient. If we are able to have
17 manufacturers willing to do this, I think this will be the
18 beginning of getting a leg up on some of these problems.

19 DR. ZUCKERMAN: I just have a quick comment. When
20 I was talking to patients, when I was doing this
21 investigation in Congress, it was really clear that people
22 contacted me who had been very happy at one point, had
23 gotten an implant, had really felt great, thought finally
24 their problem was problem was solved and then, a year later
25 or two years later, they felt completely differently.

1 That is why I made the comment earlier about long-
2 term safety data. When I said that, I didn't know what the
3 studies looked like. I never dreamed that the dropout rate
4 was so high after even two months let alone after twelve
5 months.

6 So I just want to say, based on my experience of
7 talking to patients, a year's worth of data just doesn't
8 really tell you anything about what is going to happen to
9 them. So many of these people thought, "Well, things can't
10 get worse. If my doctor says, "Try this new implant. It
11 will make you better. It is worth a try," only to find out
12 that things could get worse.

13 So that really concerns me. That is obviously the
14 purpose of doing studies with some kind of long-term follow
15 up.

16 Thanks.

17 DR. PATTERS: Dr. Zuckerman, in the people that
18 you have contacted, do you have any anecdotal experience
19 about what the percent of the success rate of TMJ implants
20 is? I am having a problem--I read letters of testimonial
21 here from people that are put in front of my that say, "Oh,
22 I have done 48 of these and every one has worked perfectly."
23 These are from oral surgeons.

24 Ms. Cowley gave me sort of a different opinion
25 that very rarely does it work well and most of the time it

1 doesn't. Do you happen to have any objective or even
2 subjective data of how many patients get better and how many
3 patients don't.

4 DR. ZUCKERMAN: Let me just be clear that the
5 people who contacted me generally were people who were
6 unhappy because I was working for a Congressional oversight
7 committee and we were having hearings and they wanted me to
8 know how bad things were.

9 We did get some calls from people who were happy.
10 They were almost always people who had implants for a very
11 short period of time. They said, "I had a terrible
12 experience in the past but now I have got this new implant.
13 I have had it for three months and I am really a lot
14 better."

15 So we certainly did hear from people like that. I
16 can't say I ever heard from a patient who had their last
17 implant or set of implants for several years and called to
18 say how happy they were. Personally, I didn't. I don't
19 have a big n. This isn't a sample. It is not a study. I
20 can only say that the people who contacted me, there was a
21 real relationship between latency, how long they had had it.

22 DR. PATTERS: In your talk this morning, you laid
23 out three criteria which you thought the panel should
24 follow. I have a feeling you knew that that didn't exist,
25 that the long-term safety and effectiveness data did not

1 exist, when you laid out the criteria that suggested that we
2 needed to see it.

3 DR. ZUCKERMAN: Honestly, it was just a best
4 guess. I actually had no idea what the data would look
5 like. I really did think that since some of these implants
6 have been on the market for quite a long period of time, I
7 really did think that there would be data for at least a few
8 years.

9 In fact, there are data for a few years. It is
10 just that there are only four people in that sample. But,
11 had the manufacturer really wanted to follow a larger number
12 of people, it seems to me they would have created incentives
13 for those people to come back instead of disincentives.

14 DR. PATTERS: I agree. I think this is an issue
15 of trying to collect data as part of clinical practice
16 versus doing an actual placebo-controlled, double-blind,
17 clinical trial which is not what was done here.

18 DR. JANOSKY: At this time, we are going to close
19 the open public hearing and move into the open committee
20 discussion and vote.

21 **Open Committee Discussion and Vote**

22 DR. JANOSKY: We have in front of us three
23 questions that the FDA would like us to answer. Are these
24 available on overhead or everyone has them? If you look
25 through your packet of information, in the agenda, it is

1 about the seventh or eighth page in the agenda.

2 Question 1. I will read the question. It says,
3 "Based on the engineering data, the sponsor has predicted an
4 implant lifetime of greater than ten years for their device.
5 Does the fatigue and wear testing presented in the PMA
6 support this predication?"

7 Panel members? General discussion or comments and
8 then I will go around assessing assessments of this.

9 DR. LI: On the issue of the engineering data for
10 implant life, I presume, actually, you calculated the
11 hundreds of years of life based on the fact that you had
12 some wear rate and then you added up the number of years it
13 would take, then, to wear away the entire polyethylene
14 component? That is kind of a nonsensical projection of the
15 life of an implant.

16 Well before you get to that point, you are going
17 to generate billions enough particles in such a small joint
18 space that I would say osteolysis is probably a given. So
19 the idea of multiplying the wear rate times the number of
20 years it takes to generate that volume of polyethylene, I
21 think is just plain nonsensical although I guess it has some
22 attraction in other realms.

23 The fatigue testing is kind of interesting. As I
24 understand it, you had a dynamic fatigue test where you
25 loaded something repetitively for millions of cycles at

1 12 Hertz and it didn't break and then, separately, you took
2 brand new implants and then you did a yield test and
3 provided a yield number.

4 Both of those tests are adequate but, typically,
5 if you really want to test this, you would have taken the
6 devices that you cyclically fatigued and then get a yield
7 strength because the issue isn't how strong it is when you
8 start. The issue is if it gets loaded that many cycles,
9 does it, in fact, lose its strength.

10 This material is relatively strong and probably
11 would have likely passed that test. But that would have
12 been a more appropriate, I think, view on that. So the way
13 I look on the dynamic fatigue test, it may or may not have
14 been a sufficient indicator. I really couldn't tell.

15 As far as the wear testing goes, I guess I am
16 troubled by the wear testing results mostly because of the
17 lack of retrieval devices. So we don't really know how
18 these things wear. I think, as Ms. Blackwell pointed out in
19 the commentary, even for hips and knees, devices which have
20 been around and tested for a lot longer, there is still no
21 really great laboratory test that guarantees that that will
22 be the performance in a patient.

23 The real test is, in fact, analysis of retrieved
24 devices or sequential follow ups on radiographic devices.
25 So I would say, in this sense, we actually don't know what

1 the wear of these devices is. But I was a little taken
2 aback looking at the individual datapoints in wear that,
3 when you assessed wear by penetration, there was a factor of
4 about 4 between your lowest wearing sample and your highest
5 wearing sample.

6 When you did it by volume, there was actually a
7 factor of almost 8 between your best-wearing and your worst-
8 wearing sample. So, as one who has done wear-testing for a
9 number of years, that is an alarmingly high standard
10 deviation for what should be a relatively repeatable test.
11 And I am unsure where the source of that data comes from.

12 But that data is where I got my earlier comment
13 that if I took your highest wear rate and then did a volume
14 calculation, you ought to be able to easily see that on a
15 radiographic analysis.

16 The fact that Dr. Mercuri doesn't find
17 polyethylene in the tissue is somewhat surprising given the
18 fact we know the implant does wear. But this may be a
19 function of how one looks at the tissue and could be under
20 the conditions that he is looking at, they are very hard to
21 see. Unless you go out of your way to see them, you
22 actually may or may not see the tissue.

23 So I put all that together saying the dynamic
24 fatigue doesn't really exactly tell me if it is going to
25 survive fatigue although Dr. Mercuri did show pictures of

1 broken plates and screws of other devices indicating that
2 there is plenty of force there to exert very high stresses
3 on this device and that the wear testing, in the best view,
4 is non-validated and, in the worst view, it does not mirror
5 what actually happens in vivo.

6 DR. JANOSKY: Additional comments?

7 DR. REKOW: The other potential pitfall to
8 complement what Dr. Li said very elegantly is that, over
9 time, wear mechanisms could change and you may get a wear
10 pattern early on that subsequently then becomes a three-body
11 problem with the particles getting in the way and creating
12 an extra problem.

13 So just to extrapolate linearly over time can be
14 dangerous.

15 DR. LI: One last issue I think which is
16 important, that is key right now in the area of total hips
17 and knees, is a method of sterilization. You picked
18 ethylene oxide as a method of sterilization which has the
19 benefit of not causing any long-term degradation to the
20 material which gamma irradiation can do if a component is
21 allowed to age prior to implantation.

22 However, the price you pay on that is that
23 several, now I think about a half a dozen hip-simulator
24 studies, have shown that if you compare an ETO product
25 versus a gamma-ray sterilized product, ETO products wear 20

1 to 40 percent higher from brand-new components.

2 So the question is, without knowing how retrieved
3 devices fail--in other words, if they fail by a mechanism of
4 delamination, pitting or fracture and not wear, then ETO
5 would be very appropriate. However, if they are failing
6 over long term because of wear mechanisms, then the ETO
7 sterilization, in fact, would not be the recommended method.

8 DR. JANOSKY: Additional comments or responses?

9 Question 2. "Wear particles generated from
10 previous implants have proven to be problematic. Does the
11 wear testing demonstrate that this device has adequate
12 safety in terms of wear?"

13 Panel members?

14 DR. LI: I guess this is really a shorter answer
15 to the question if you don't have any--I'm surprised that,
16 given the number of laboratory wear tests that you did, that
17 you didn't once, at least, look to see if the particles are
18 of the appropriate size.

19 For instance, it would be a good validation of
20 your test if you generated particles of the same shape and
21 size as found in vivo and, in fact, it would be a good
22 reason to completely ignore the test if the particles that
23 were generated were, in fact, different in size and shape
24 than found in vivo.

25 So, in the absence of that data, it is another

1 question--you have got a big question mark you have got to
2 put over the laboratory data about whether or not it was
3 appropriate. So the lack of that information, I don't think
4 there is any way would could tell anything about the fate of
5 these particles or how many were generated or anything along
6 those lines.

7 DR. JANOSKY: Additional comments, responses?

8 Moving on the question 3. "Do the data
9 demonstrate reasonable safety and effectiveness when taking
10 into account possible risks and benefits to the patient?
11 Please state the basis for your answer."

12 Let's start this way and work our way around.

13 DR. PATTERS: Quite clearly, some patients do
14 benefit from this device. I think that that has been very
15 well shown. However, a lot still is unknown. I do not
16 believe that effectiveness data can be generated in the type
17 of clinical research that has been performed to date because
18 it is all--in my mind, it is quite anecdotal and it is a
19 series of anecdotes taken from a whole bunch of different
20 practices following a protocol but, really, it is part of
21 clinical practice and it is not defined separately for
22 research.

23 For instance, in periodontology, when we test a
24 device, the manufacturer sponsors that test and we pay
25 patients for their inconvenience to come back for our follow

1 up. In that way, our purpose in doing this is actually to
2 test the device in a double-blind, placebo-controlled
3 clinical trial and get all the data that is possible.

4 That is not what was done here. These were
5 implants that were placed in patients who clinicians
6 believed, in their clinical judgement, would benefit from
7 these and data was collected as possible in that framework.

8 I don't think you can really develop
9 scientifically valid data if that is really your only
10 measure. So, quite clearly, I think people benefit. The
11 long-term data is not here regarding the effectiveness in my
12 opinion and a lot remains to be done.

13 I would not like to see this alternative for
14 patient care removed. But I believe this alternative needs
15 to be available. However, it needs to be presented to
16 patients, I think, as a treatment of last resort with a
17 relatively high failure rate.

18 DR. GONZALES: I feel that the pain measures were
19 not done properly in my mind. Efficacy for pain reduction
20 was not determined. Therefore, I think you have to throw
21 out the pain data. At least, I'm less strong in terms of
22 function and diet in terms of the measures, but certainly
23 for the pain measures, it was not done properly.

24 I don't feel that this device is efficacious for
25 pain in patients with ten or greater prior surgeries and,

1 therefore, those patients should be excluded or those
2 patients should be warned that this procedure is not a
3 procedure for pain reduction.

4 I think that if this device is approved, it should
5 be approved with those conditions.

6 DR. REKOW: In spite of what you said about
7 double-blind placebo studies which, I agree, are ideal, I
8 don't see how you could conceivably do one of those when you
9 have radiographs that show quite clearly which device you
10 have in place. So there are some practical issues with this
11 design of the study.

12 But, having said that, I am concerned with the
13 amount of data that is available for patients who clearly
14 are most likely going to have a device for a very, very long
15 time. I, too, think that it has its place. There are some
16 patients that need it but I don't think that we can clearly
17 say that the patient who is between 35 and 45 can look
18 forward to a pain-free life for a really long time with this
19 device.

20 I don't think that the data, as presented, shows
21 that clearly.

22 DR. HEFFEZ: I think you have to separate safety
23 from effectiveness. I think what is most important is
24 safety. The effectiveness is hard to judge because every
25 patient has a different constellation of symptoms that one

1 has to address. For me, the primary thing to look at is
2 safety.

3 I am concerned that the construction of
4 prospective studies that are currently underway, that study
5 protocol needs to be looked at or we are just going to amass
6 data that is still going to be difficult to interpret later
7 on.

8 Do we need such an option? I think we do and I
9 think that this option should have certain exclusivity and I
10 do think that it should be looked at possibly as a temporary
11 device, temporary meaning five to ten years. On other
12 words, the patient should be aware that the likelihood of
13 replacement is there.

14 The key, as far as safety is concerned, is, I
15 believe, are we able to retrieve this device with minimal
16 damage to the patient, any damage being local and not
17 systemic and that it does not remove the ability to
18 reconstruct the joint at a future date.

19 DR. BERTRAND: These are a desperate group of
20 patients. What we haven't done is really characterize how
21 or what these patients are suffering or how this has
22 affected their lives before we do something to them again.
23 I think it is really incumbent upon us, if we are going to
24 use devices like this, to really characterize what that
25 patient is experiencing, how they view what they are going

1 to do in the future, whether types of situations affect who
2 they are.

3 There are instruments that can measure that,
4 predictably and reliably that would address what Dr.
5 Gonzales was talking about, the effect of pain and what the
6 pain is upon their lives. I think that has to be done from
7 the baseline and has to be done with follow ups.

8 Additionally, dealing with these types of patients
9 on a daily basis, there are some patients for which an
10 ankylosis does need some type of appliance to be placed to
11 help that people. So this looks like we have pilot data for
12 this point. And we really don't know the long-term
13 effectiveness. I would hate to close the door on this at
14 this point, but I think definitely think we need to
15 characterize the patients more thoroughly at every juncture.

16 DR. LI: Just an issue on the length of follow up,
17 and again, to follow up Dr. Bertrand's question. Typically,
18 an orthopedics, larger joints in orthopedics, osteolysis
19 takes a minimum of about four to five years to occur. It is
20 highly rare to get osteolysis in the short times of the
21 clinical follow up provided.

22 So, as far as the long-term consequence of the
23 wear, it is virtually unknown for this device. It may or
24 may not be an issue but we can't tell by the follow up
25 presented so far.

1 DR. BURTON: I think that, again, we have a device
2 which is necessary in terms of treatment of a small group of
3 patients. But I am not sure that the data we currently
4 have--I think it shows some safety but we don't know the
5 long-term safety issues because we don't know what those
6 wear byproducts are, how much they are going to accumulate
7 and what their long-term effect is going to be.

8 Secondly, we are not sure about the effectiveness.
9 I think that is what Dr. Bertrand and Dr. Gonzales were
10 alluding to. I think that this product needs to be there.
11 The question is whether patients are made aware of what its
12 true effectiveness. It may be functionally effective in
13 terms of dealing with range of motion and potentially
14 masticatory issues, but, again, this is a very definite
15 group which may be driven more by pain in many cases than it
16 is strictly by functional issues.

17 They may be getting something which may be
18 effective in addressing a portion of the problems but
19 ineffective in dealing with the other ones, and they need to
20 be made aware of that such that when they are making the
21 informed-consent process, they are truly aware of when we
22 say it is effective what it is effective for.

23 DR. JANOSKY: Additional responses, comments?

24 DR. STEPHENS: I think that clearly some type of
25 temporomandibular-joint replacement is absolutely

1 essentially. I think that part of the effectiveness problem
2 is that I don't know that you can expect to have a
3 consistent effect in this group of patients because they
4 have such a wide group of symptoms and etiology.

5 My experience with total-joint patients is that,
6 after two or three operations, somewhere along the line, the
7 percentage of them that have, as an example, neuropathic
8 pain associated with this disease is very high and that even
9 in patients with joint replacements, these symptoms are
10 going to persist after the joint is in place.

11 I think the key is what this therapy is mated to
12 is most important. I think the joint replacement benefits
13 are fairly predictable. The intra-articular pain that
14 patients have from sclerotic bone against bone is likely to
15 improve and the stability of their occlusion is likely to
16 improve.

17 But a lot of these side issues, the neuropathic
18 pain, muscular pain, problems are not going to be--there is
19 not going to be a level effectiveness. So I think that we
20 definitely need the devices and we probably will need
21 additional studies in whatever way that it is approved.
22 Hopefully, it would be approved and we would need additional
23 studies to go with it.

24 DR. JANOSKY: Dr. Runner, are there any additional
25 questions you would want us to consider at this time?

1 DR. RUNNER: I would just say that, in your
2 deliberations, you should be very specific in terms of what
3 you would like.

4 DR. JANOSKY: Okay. Before we move for a motion
5 and a vote, are there any responses from the sponsor or a
6 few minute for final comments.

7 MR. ROSE: I have several comments I would like to
8 make. I would like to address Dr. Li's questions about
9 characterization of the wear particulates. I have to
10 confess I am not current on the literature at what point
11 wear particularization became an important feature. This
12 wear study was done quite some time ago.

13 To that end, it may have preceded a lot of the
14 recent knowledge that has been developed in that area on
15 wear particulates. This device was developed as a salvage
16 procedure to deal with conditions that exist. It was not a
17 device that was developed to see if a market could be found
18 for it. It had a definite indication in a situation that
19 really had very little alternative.

20 In earlier discussions here, I think people have
21 mentioned that there was only--we have dwindled to four
22 patients, or very small numbers and a very short number of
23 years. We did present information that we have 29 patients
24 that we followed out at the seven-to-eight-year time frame.
25 So we do think we have an indication at least that the

1 device is lasting for a long period of time and it is
2 functioning for some people and it is greater than four.

3 This device also suffered for a period of time in
4 which there was no sponsor. There was nobody to be
5 following up that information and actually it was never
6 known at that point if it was ever going to be made
7 available. So I think a situation existed where there has
8 been a lot of effort to collect the data that has been
9 shown.

10 I agree that it is not optimal and it is not done
11 in an appropriate research method, but I think there is
12 evidence or indication at least that there is some value
13 that has been obtained on this.

14 As far as the comments about pain, it has never
15 been our contention that this eliminates pain. In fact,
16 that is one of the reasons that this was done by the group
17 of clinicians who was looking at that, is they wanted to
18 find out how it was effective for people and the fact that
19 the larger the number of surgeries, the pain level has
20 statistically been shown to be reduced.

21 It just hasn't been reduced to as great a level of
22 those patients who have fewer prior surgeries. This
23 information has all been included in our literature that we
24 have developed directly for patients to inform them of that
25 exact condition. I don't remember who brought that point up

1 but there has been a strong effort to label this device
2 appropriately so that patients are fully informed of the
3 risks and the problems they might encounter.

4 We think that has been very important given the
5 past history of patients having unnecessary surgery or
6 surgery and they weren't really understanding what was
7 taking place or what implants they were about to get. We
8 take that very seriously.

9 Function is something we aim to restore. We know
10 that there are problems with pain restoration. But, for
11 many of these patients, I have spoken with them personally.
12 They say they have realistic expectations. They understand
13 that they are going to be living with pain for the rest of
14 their lives and they say, "I just need some functioning."

15 They have a realistic expectation that that is the
16 best they can hope for at this point given their surgical
17 history.

18 Those are all the comments I have.

19 MR. ULATOWSKI: I have two comments. The first
20 comment is I certainly want to remind the panel about the
21 discussion this morning regarding valid scientific evidence
22 and the flexibilities provided under the regulations on what
23 might be considered to be such type of evidence and the
24 types of devices we are dealing with today in terms of the
25 history of marketing of the products, availability of the

1 products.

2 I think there is another aspect here. As you move
3 toward your vote, you will be voting up and down depending
4 on what the applicant has presented to you today or
5 tomorrow. I think it is going to be helpful to the FDA
6 that, if there are areas of problems in terms of the data or
7 the types of patients, concerns that you may have, if you
8 have directions for us in terms of in what subpopulations or
9 what conditions or what areas there might be viability to
10 this product or other products that will come along, certain
11 labeling restrictions, other areas that will help us in some
12 scientific negotiations or other discussions with the
13 company so we can perhaps seek an acceptable middle ground
14 with the company on a condition of use.

15 So although companies tend to come to you asking
16 for the whole ball of wax, quite often there is a niche
17 there, there is an element of acceptable performance and
18 knowledge base that would be worthwhile. So, in your
19 discussions, consider that.

20 DR. JANOSKY: Dr. Floyd, do you have some comments
21 for us being the industry representative?

22 DR. FLOYD: It has been a very interesting
23 discussion. From my perspective, obviously, my background
24 is not orthopedic surgeries or joint-replacement surgeries.
25 But I do have a strong engineering background and a strong

1 anatomic pathology background.

2 The thing that has impressed me about this is we
3 are dealing here with a poorly characterized disease
4 process. We have heard a lot of anecdotal patient
5 information that I think all of us can sympathize with and
6 react strongly to. On the other hand, much of that
7 information does not directly relate to the condition and
8 the device we are talking about here.

9 We are talking about a device that is really for
10 rescue of the patient for which there are very, very few
11 other options. We are talking about a device that is built
12 upon--and, remember, it is a preamendent device--but it is
13 built upon a lot of information derived from other major
14 joint-replacement mechanics, engineering. We can quibble
15 about the engineering data and I appreciate all those
16 arguments.

17 However, we have a device that has a couple of
18 very unique--one extremely unique property and that unique
19 property is tailoring to a patient who has had severe
20 anatomical changes from surgery or other disease processes.
21 And, therefore, we have a device that is custom for that
22 patient and, in fact, may be the only kind of option that
23 patient has at this particular time to have any semblance of
24 function.

25 I don't think anyone has ever claimed that the use

1 of this device will return a patient to their pre-disease
2 state. In any of the medical specialties that I am aware
3 of, it would be foolish for any practitioner to ever claim
4 that to a patient because we don't have those kinds of
5 capabilities are our fingertips at our current state of the
6 art.

7 But what we are talking about here is a device
8 that, for a limited number of people, may be the only option
9 possible. We have heard that there is a mechanism in place
10 to track these patients, to follow up data. And we have had
11 a suggestion from the company, and I suspect the FDA will
12 reinforce this, that that follow up will become even more
13 strenuous in the future so that we will collect some of the
14 data that we don't have at the moment.

15 I am a non-voting member of this group but I would
16 urge all of us to seriously consider what the options are
17 for these patients and what the threat of this device is
18 because we are talking about safety and effectiveness--what
19 the threat of this device is for this limited subset of
20 patients who really do have very few other alternatives.

21 DR. LI: Maybe one question for the dental
22 surgeons or maybe Dr. Mercuri; if, down the road, it turns
23 out--let's say that worst of all worlds happens and, for
24 some reason, this device actually does cause osteolysis at
25 five, six or seven years when you get out to several hundred

1 patients at that time.

2 So now you have a patient that originally came in
3 with a compromised joint and you are going to put this
4 device. The ramification of osteolysis is loss of even more
5 bone. Now, if you try to move the device, you are going to
6 have lots of screws in there as well.

7 So I guess my question is what would the surgical
8 or the medical treatment be on a patient that got one of
9 your devices and, heaven forbid, got osteolysis out in eight
10 or nine years and you had to, then, do something.

11 DR. MERCURI: It is a good question. I think the
12 patient-fit aspect of this device--in other words, I showed
13 you some clinical examples of devices that had failed and
14 left the patient with basically no ramus and those are the
15 kinds of cases that a patient-specific device is made to
16 deal with.

17 In your own field of orthopedics, when you have a
18 hip that has had a device fail where you have lost the stock
19 bone, you go to a "custom" device to be able to deal with
20 that situation. So I would say that this is the perfect,
21 although in this world there is nothing perfect, but this is
22 certainly the alternative for a patient who would be in that
23 situation and where you are seeing those patients right now.

24 We see patients with other devices that have
25 failed that we are now able to give a semblance of function

1 to that they would normally not have because there is no
2 other device available right now that can handle that
3 situation.

4 DR. REKOW: But what happens when yours fails?
5 Then what does the patient do?

6 DR. MERCURI: I look at this as an evolutionary
7 process. I am not talking about evolution of this
8 particular device. We have talked about that enough today.
9 But I look to the future as there being an evolution to
10 maybe the next level of biomnemics, maybe the next level.

11 DR. REKOW: Can you get yours out?

12 DR. MERCURI: I have not had to take one of mine
13 out. I can tell you that the people that I mentioned before
14 who had removed the device were able to remove the device
15 without doing significant damage to the underlying bone.

16 DR. PATTERS: I think what I am troubled mostly by
17 is I have not been able to get a handle here on what the
18 true success rate is, whether patients five years after
19 treatment, whether the majority feel benefit from the
20 treatment or feel worse from the treatment. I just don't
21 have a good handle on that from the discussion.

22 I do hear, over and over again, about people being
23 on their fifth set of TMJ implants. That is obviously four
24 sets that have failed. And that is of great concern to me.

25 DR. MERCURI: Is that a question?