

1 better than 80 percent.

2 And even to kind of add to my patient
3 accountability slide, I don't know if you noticed,
4 but at the four years we had the best follow-up.
5 There were only, I think, 23 patients out to four
6 years, but the investigators made *an* extreme effort
7 to try to get all of the patients back in the three-
8 year follow-up.

9 In some cases it took almost a whole
10 year to get them in. So actually we got a higher
11 follow-up at four years, and actually three of the
12 patients that missed the three-year follow-up were
13 actually seen at the four-year. I think I did that
14 calculation.

15 If I combined and made a three-year plu
16 and added those four years, the follow-up, I think,
17 was bumped up to 87 or 88 percent, even at three
18 years, which was the lowest follow-up.

19 So we did have greater than 80 percent
20 then.

21 DR. JANOSKY: Let me get more specific
22 with my question. If we think that you started with

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1 180 patients in the study, at what point did you
2 have 80 percent follow-up of those 180 patients?
3 Complete data, 80 percent of them. At what point
4 was that?

5 MS. VERSTYNEN: The thing **is that only**
6 at the one month time point were there 180 patients.

7 DR. JANOSKY: **Okay.**

8 MS. VERSTYNEN: Well, no. Actually only
9 at the baseline were there 180 patients because
10 enrollment is occurring as we speak. I'm guessing
11 Dr. Quinn did cases this week. So if you even
12 looked at the one month, there were already ten
13 patients who had missed follow-up because one of the
14 requirements in my data cutoff was that each patient
15 should have at least been for their one month
16 follow-up.

17 So even at the one month, we had ten of
18 the 180 that missed.

19 DR. JANOSKY: Okay. So you're down to
20 95 percent at that point.

21 MS. VERSTYNEN: Right, exactly.

22 DR. JANOSKY: So I understand that you

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1 have rolling enrollment. That's typically how we do
2 clinical trials in also this type of forward looking
3 study.

4 But my question is at what point do you
5 have 80 percent complete data of those 180,
6 irrespective of when they were due. So at **what**
7 point do you have 80 percent of 180 patients?

8 MS. VERSTYNEN: I calculate the **six**
9 month point.

10 MR. CANNER: Maybe we're on the same
11 wave length since I'm a statistician, too, but
12 that's a joke.

13 DR. JANOSKY: I didn't hear your name
14 earlier.

15 CHARMAN HEFFEZ: Yeah, identify
16 yourself.

17 MR. CANNER: Sorry. Joe Canner, a
18 statistician with Hogan & Hartson.

19 I think what you're getting at is take
20 80 percent of 180, which is -- I can't do the math
21 in my head -- maybe 140 or 150 or whatever, and when
22 those patients would all have three-year follow-up.

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1 I don't know the answer to that, and I
2 think Mary, now that she understands what the
3 question is, can answer that. But I think probably
4 the more relevant answer is that the original sample
5 size calculation for the study was only 86 patients,
6 and FDA has granted Biomet permission to enroll 300
7 patients altogether, but 86 was the original **sample**
8 size.

9 So I think probably a more relevant
10 question would be when 80 percent of the patients
11 will have reached three years among the first 86,
12 and as you can see, we're already up to close to 50,
13 and so that time frame is probably not very far off,
14 although Mary could probably answer that a little
15 bit better.

16 DR. JANOSKY: I understood the primary
17 endpoint to be three years.

18 MR. CANNER: That's right.

19 DR. JANOSKY: So my question then is at
20 what point do you have 80 percent, which is a
21 liberal follow-up level?

22 MR. CANNER: Of the **86** that were

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1 originally anticipated?

2 DR. JANOSKY: Of the 180 that were
3 enrolled, and that period of time is at the six
4 month follow-up. If you're going to go with 86,
5 what are you choosing? The first 86 that were
6 enrolled?

7 Then we get into the issue **of what** were
8 cemented and what were not cemented, and some of the
9 other issues, but we can leave this point because
10 I'm sure it's going to go throughout the day.

11 MR. CANNER: Yeah. It's just that --

12 DR. JANOSKY: But what if we return to
13 the second point. The second point that I had
14 mentioned is that at that point that you have 80
15 percent follow-up, which is the six month point,
16 what percentage of the patients at six months are
17 Dr. Quinn's and what are Dr. Sinn's?

18 It's essentially zero. **So** we can leave
19 that out. So what percentage are Dr. Quinn's? What
20 percentage are Dr. Sinn's at the six month point?

21 MR. CANNER: Okay. I'll have to look
22 that up for you now that I understand what you want.

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1 DR. JANOSKY: Okay. I'll return to the
2 issue later so that we can.

3 CHAIRMAN HEFFEZ: Dr. Patters.

4 DR. PATTERS: Mark Patters.

5 A question for Ms. Verstynen and perhaps
6 Dr. Quinn. One of the issues that FDA charges the
7 panel is to make a determination **as to** whether the
8 data in the PMAs support the safety and
9 effectiveness of the device for its indicated uses.

10 You have in your labeling ten indicated
11 uses, but my review of the data says that some of
12 the indications have no data or minimal data, such
13 as use in malignancies or the nonneoplasms. How is
14 the panel to look then at whether there's safety and
15 efficacy and effectiveness are supported for that
16 specific use?

17 DR. QUINN: That's an excellent
18 question. I think what we have to do is put the
19 numbers in perspective, first, in terms of the total
20 potential market for a safe and effective
21 prosthesis. I think there are 450,000 hips done a
22 year. Nobody has a very precise way of predicting

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1 what **is** the total. population, but I've heard
2 anywhere between 1,500 and 2,500 a year. It defines
3 a very small population to begin with, which I think
4 is appropriate. I don't think this should be widely
5 used unless there were indications.

6 The more common indications that you saw
7 are osteoarthritis, traumatic arthritis, ankylosis.
8 I think it is reasonable to assume that if a
9 prosthesis is safe and efficacious because the
10 surgical technique would be very similar in a
11 multiply operated joint who has had seven
12 operations, in a joint that has an osteochondroma
13 where there's been no surgery, I would be
14 comfortable making that assumption that it's safe
15 and effective and that indication.

16 The problem is the numbers. I've
17 probably seen two osteochondromas in 15 years. So
18 I'm not sure whether we'll ever be able to answer
19 that question with the appropriate numbers.

20 DR. **PATTERS**: I guess my concern then:
21 should that be included in the labeling **as** an
22 indication or should the labeling state that there's

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1 no data available for treatment of bases with
2 malignancies?

3 DR. QUINN: I think I'd leave that to
4 somebody more expert in labeling. Does that allow a
5 reasonable surge in the off label indication to use
6 the prosthesis in that rare instance? Because I do
7 think that should be the ultimate outcome for a safe
8 and effective prosthesis.

9 DR. PATTERS: I'm not an expert in the
10 off label use, but my understanding is that off
11 label use by the practitioner is always available.
12 You know, they accept the liabilities when, of
13 course, there is no specified use in the labeling.

14 DR. QUINN: Yeah, I'm not sure I'm
15 expert enough to answer it other than what I've
16 said.

17 MS. VERSTYNEN: Mary Verstynen.

18 It would be reasonable to add that
19 language to the labeling, and if FDA would agree
20 with that, I mean, it would be reasonable because we
21 don't have malignancies. We probably don't have any
22 benign neoplasms or very few, and maybe we need to

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1 qualify that directly in the labeling with either
2 little or no clinical data.

3 It's a reasonable request.

4 DR. PATTERS: Thank you.

5 CHAIRMAN HEFFEZ: Dr. Cochran.

6 DR. COCHRAN: David Cochran.

7 I had a question **on** the radiographic
8 analysis. It said that the heterotopic bone
9 formation was evaluated osseous erosion and fossa
10 resorption. So certainly when you deal with bone
11 and screw into bone, and I think the question was a
12 little bit earlier about screw loosening was never
13 answered.

14 Was the radiographic analysis
15 standardized or was it done under blinded condition?
16 And how as each of those aspects addressed?

17 DR. QUINN: Yeah, the radiographic
18 analysis was a Panorex lateral ceph. and a PA ceph.
19 They're standardizing such that sites with the same
20 machines are used. I'm not sure you can standardize
21 them any more than that.

22 As you know, it's difficult because they

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1 are -- at best Panorex is an elliptical tomogram.
2 You are looking for gross osteolysis or gross
3 radiolucencies around them. It is difficult because
4 there's metallic objects. So it would be probably a
5 gross malposition that you would pick up.

6 The heterotopic bone was probably the
7 easiest finding, but the X-rays were standardized to
8 those three views. Does that answer the question?

9 DR. COCHRAN: Well, from a
10 standardization, but did Dr. Sinn do the same
11 radiographs at each **of** the same time points? That's
12 what I mean by standardization. In the protocol
13 were set radiographs taken at set time points?

14 DR. QUINN: Yes.

15 DR. COCHRAN: And then from a screw
16 loosening point of view, the fossa component is the
17 plastic. So that isn't going to get in the way of
18 looking at screws and positioning of screws. I just
19 wondered if there was like a third person or a
20 radiographic investigator who would evaluate the
21 position to see if they had changed.

22 I think in some of your cases there was

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1 some movement in some of the components. I just
2 wondered if there was an independent evaluator to
3 evaluate the X-rays.

4 DR. QUINN: Well, as I said, we had no
5 device failures. We had no screws, and we had
6 change in the position, but that **was gross**
7 dislocation. That wasn't movement of the prosthesis
8 itself.

9 The only finding of note was the
10 heterotopic bone formation. I could let Dr. Sinn
11 address if he followed it the same way, but they
12 were the standard three radiographs based on the
13 baseline films taken postoperatively in the hospital
14 at each landmark.

15 Now, at the times when we had patients
16 refused, like for example pregnant patients, we
17 documented that there was a visit without
18 radiographs.

19 MS. VERSTYNEN: I think to answer that
20 question more directly, with some of our newer IDEs
21 it has become a major issue, and included into our
22 protocols that we have independent radiographic

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1 assessments.

2 This IDE was filed in 1994, and we
3 weren't quite that sophisticated to add that to the
4 protocol. Therefore, each of the investigators did
5 their own radiographic assessments.

6 DR. BURTON: Richard Burton.

7 A question for Dr. Quinn. On your
8 technique portion which you published, **and** Step 4
9 talks about performing an osteotomy, and they have a
10 traditional condylectomy, and then once you're able
11 to retract the stump down, it talks about removal of
12 a larger segment of the condyle, and it wasn't clear
13 in reading some of the other surgical materials
14 whether or not a coronoidectomy was included with
15 that.

16 Then in your adverse events there were
17 15 joints that required an additional coronoidectomy
18 to improve I would assume range of motion associated
19 with that.

20 **Is** that a long enough time frame out
21 that there was regrowth, reformation of the
22 coronoid? And is that actually a standard portion

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1 of the procedure *is* a coronoidectomy?

2 DR. QUINN: It's not a standard. I
3 think in the multiply operated joints where they
4 start with large restriction of motions, I'd
5 recommend that the way to do the two-step osteotomy
6 is the second osteotomy is to include the coronoid
7 in it in a one piece step, and we've designed
8 instruments to do that.

9 I do think that the 15 cases show that
10 early on there are probably cases where we should
11 have removed it because you have the option of
12 making almost a C cut. The way you determine how
13 much bone you take off is once the fossa implant is
14 in place and you put the patient in fixation, if you
15 haven't removed enough bone, you will actually hit
16 the lip of the implant with the superior edge of the
17 ramus. That determines how much bone is removed.

18 I think it's surgeon dependent whether
19 they determine whether to take the coronoids off at
20 the time. I think in multiply operated patients who
21 start with a ten millimeter size, I would remove it.

22 If they were largely being operated on

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1 more for pain than mechanical obstruction, it's not
2 necessary that all of the coronoids have to be
3 removed.

4 DR. BURTON: Okay. Thank you.

5 CHAIRMAN HEFFEZ: Dr. Li.

6 DR. LI: Steve Li.

7 I have a question for **the** designers of
8 the device, perhaps Mr. Roman.

9 The one thing that I'm a little
10 uncomfortable with in your prosthesis design and the
11 fossa design is -- let me make sure I understand it.
12 The fossa component is fixed with what, five screws
13 through the polyethylene to the bone?

14 MR. ROMAN: That's correct.

15 DR. LI: So typically we don't -- I
16 would say generally designers typically don't fix
17 polyethylene directly with screws. When the
18 polyethylene would be under load because of the
19 creep that's going to occur, and **so** on the fossa I
20 would never expect the bone screws to pull out
21 because if there's any load on the polyethylene, the
22 polyethylene is going to creep and essentially make

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1 the screw holes bigger and the fossa component would
2 become loose.

3 So in general, you never see or hardly
4 ever -- this is the only device I've ever seen where
5 the polyethylene is actually screwed to the bone to
6 accomplish the load.

7 So my question is: have you ever looked
8 at the change in the fixation of the polyethylene to
9 the bone before and after loading?

10 And perhaps, Dr. Quinn, if you've ever
11 noticed on retrievals if the polyethylene component
12 **is** actually looser than it was, because we see this
13 on total hips and total knees. Even after a six
14 month period if you do a measurement of the fixation
15 of the polyethylene to a metal backing, that
16 fixation loosens relatively rapidly even when the
17 whole component is fixed, and now you've got five
18 individual screws that are much higher stress
19 concentrators.

20 So I would predict that eventually that
21 polyethylene would become loose from the screws, and
22 that's a long way to ask: have you ever looked at

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1 that? And *is* there a way to measure that off of
2 your fatigue tests?

3 DR. QUINN: No. That has not been
4 looked at specifically, but the design of the fossa
5 screws does have a flat portion on the under side of
6 the head that serves as basically a washer. So we
7 are basically sandwiching the polyethylene between
8 the under side of the head and zygomatic arch.

9 As far as if that's been looked at from
10 explants, I don't know.

11 DR. QUINN: No. The four that were
12 removed were for infection, and we didn't find any
13 loose screws or mobility in the fossa implant
14 itself. Just correction. It's a minimum of four
15 screws. They had 2.0 millimeter, and they were
16 designed, especially designed 2.0 millimeter with a
17 broader head to give that washer effect.

18 DR. LI: But that won't affect creep in
19 the superior/inferior direction, will it, unless
20 I've got my orientation wrong?

21 In other words, you know, it's a three
22 dimensional piece and that washer effect protects

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1 you in one direction but not the others, and if the
2 polyethylene is loaded against the screw, it's going
3 to creep.

4 And so the chance, I think, of it
5 remaining tight forever is near zero. **So** it may be
6 tight enough to be clinically successful, but I
7 can't imagine that it's after a million **or** 500,000
8 loading cycles that it, in fact, is fixed with the
9 same tightness it was at the moment you fixed it.

10 DR. QUINN: I'll let Shawn answer it. I
11 didn't see any clinical, but I obviously am not
12 examining for creep in the screw holes when we have
13 removed them. I don't know whether the test was
14 specifically done because it was done at an offset
15 to see if we would fracture it at the junction
16 between the horizontal and perpendicular aspect of
17 it, and I latched on to see if there was any other
18 test done other than seeing whether it fractured.

19 DR. LI: Well, for instance, on that
20 test you mentioned, had you measured the amount of
21 micro motion before and after that test, you might
22 have gotten some indication for if it's going to

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1 loosen, but that you have to measure because
2 remember 100 microns is more than enough to cause
3 sufficient motion to change the biomechanics and the
4 wear properties.

5 So this might not be something you could
6 casually feel. You would actually have to go in and
7 measure it and actually see, but the effects could
8 be cumulative, very large.

9 DR. QUINN: Measure it in vivo or?

10 DR. LI: In vivo is tough, but even in
11 the laboratory test you could make some attempt to
12 measure that, but certainly clinically as these
13 patients get out longer, when you get out to five,
14 six, seven years, I think that would be something I
15 recommend you **look** at very carefully, is the
16 fixation of the plastic component.

17 The screws are going to be intact. It's
18 the plastic, I think, that's going to move
19 independently of the screws.

20 CHAIRMAN HEFFEZ: I'd like to move on
21 with Ms. Helms and followed by Ms. Howe.

22 MS. HELMS: Thank you.

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Elizabeth Helms, and I'm going to follow up with the loading issue because I think it's so vitally important, especially since I'm a patient that had two open joint surgical procedures, condylectomy and no implantation and have done really well.

But you know, malocclusion *of* a Class II or Class III, where there is a deviation or an asymmetrical mandible, was the testing done other than just rotating? Was there testing done where the job deviates, where that would increase the load on that joint and allow the joint to move at that deviation point?

That's my first question and you can respond to that.

MR. ROMAN: I did want to clarify from the earlier discussion of the fatigue testing. As I discussed, in the testing the mandibular components were angled at a ten degree angle to place them in a worst case scenario, both subjected the ramal plate to a large bending moment, and **also** minimized the surface contact between the spherical head of the

1 mandibular component and the spherical seat of the
2 fossa component.

3 MS. HELMS: Okay. Then were there any
4 studies done in the follow-ups where there was a
5 unilateral joint? Was there any degeneration or
6 increased stabilization to the opposite joint?

7 MR. ROMAN: Let me **go back** because I
8 think Dr. Hefez raised the same issue. I think
9 it's a very important issue. When we placed the
10 condyle in the fossa, I don't know of any
11 methodology to know exactly what happens to that
12 seating. The relationship to the condyle and the
13 fossa, which I think is what Dr. Hefez was getting
14 at, when this patient now wakes up, has muscle tone
15 and functions.

16 I doubt it's in the exact place we place
17 it surgically. That would be counterintuitive. The
18 reason we designed the condylar head as such a
19 large, spherical head is to allow for some of that
20 because I think it's impossible for us to know at
21 the time of surgery that this is exactly where this
22 patient will function.

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1 Your second question is a very
2 interesting one, and that is when you place a
3 prosthesis unilaterally and you have a normal
4 functioning joint that has a lateral pterygoid,
5 you've got two different tires on a car.

6 I mean, I've heard surgeons who are much
7 more aggressive than I am say if you put one in, you
8 should put both in. I think that's overly
9 aggressive.

10 Theoretically they would function better
11 because you would have two systems that have no
12 rotation and -- I'm sorry -- translation and just
13 rotate. I think there's a point at which when you
14 send patients for physical therapy after joints
15 especially unilateral, I'm less concerned with
16 achieving 30 millimeters. I'm worried about people
17 going further. These aren't designed to do that.

18 And I think it's more problematic when
19 you have one prosthetic joint and one natural joint
20 because at about two thirds of the opening, you
21 start to get the lateral pterygoid muscle on the
22 contralateral side take over. The prosthetic joint

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1 stops moving, and **you** see deviation.

2 So our bigger problem is we've been
3 surprised how good the results are in increasing the
4 intercisal opening. I'm worried by people who say,
5 "I think I can go to 40 millimeters," because I
6 don't think these joints are designed to do that,
7 and it's more of a problem in the case you describe
8 where there's a prosthesis and an otogenous joint.

9 Does that answer your question or is
10 that --

11 MS. HELMS: Half way.

12 CHAIRMAN HEFFEZ: Ms. Howe.

13 MS. HOWE: Elizabeth Howe.

14 My question is kind of a blend of both
15 the need to do professional training as well as this
16 lost follow-up, the question being: was there any
17 thought given to using sites three and four to do
18 follow-up data collection enabling people who might
19 be on the other side of the country to actually have
20 that data collection done?

21 DR. QUINN: No. It's a good suggestion.
22 We did not do that.

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1 CHAIRMAN HEFFEZ: Dr. Hewlett.

2 DR. HEWLETT: Edmond Hewlett for Dr.
3 Quinn again.

4 Your presentation as well as the
5 proposed labeling indicate that occlusal
6 relationship changes may, in fact, occur as a result
7 of the placement of the prosthesis. In your
8 protocol was there any provision made for assessing
9 occlusion postoperatively and then treating any
10 potential interference, say, with a splint in order
11 to eliminate occlusion as a possible etiology in the
12 adverse events?

13 DR. QUINN: Part of the follow-up form
14 is the occlusion checklist. What's the intercisal
15 opening? Is there an open bite? **Is** there a **cross**
16 bite? That's part of all the landmarks.

17 The question is: was the preexisting
18 occlusion secondary to the temporomandibular joint
19 or vice versa? And that's a chicken and egg
20 question I don't think anybody can answer.

21 The point we made with the prosthesis is
22 you have the ability to change the occlusion. So if

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1 you started with what we've seen, some of the
2 idiopathic female condylar resorption, where we see
3 females, late 20s, early 30s, who have marked
4 resorption of condyles that become Class 11, there
5 you know that the malocclusion was secondary to the
6 temporomandibular joint disease, and there's a case
7 where I think if we were going to **place** the
8 prosthesis, we would try to improve the occlusion.

9 I don't think we would just try to
10 improve everyone's occlusion who had a prosthesis,
11 but when the malocclusion is secondary to the
12 temporomandibular joint disease, it is something
13 that you can address with the prosthesis.

14 CHAIRMAN HEFFEZ: Is your question
15 answered, Dr. Hewlett?

16 DR. HEWLETT: Well, I guess. Yeah,
17 maybe just to clarify, I think I'm referring
18 specifically to any assessment in addition to the
19 assessment they outlined. Any functional
20 assessment?

21 DR. QUINN: Oh, I'm sorry. Yeah, it is
22 common, and it wasn't something we reported because

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1 I do think it's part of normal post surgical that we
2 do occlusive adjustments. If somebody came in two
3 months later and had a very high contact on a
4 canine, we will adjust it.

5 Most of these patients, we try to get
6 them off splints.

7 DR. HEWLETT: I see.

8 DR. QUINN: If at all possible.

9 CHAIRMAN HEFFEZ: A couple of quick
10 things, and then I'd like to move on to the FDA
11 presentation.

12 One is at one point in time you were
13 removing the peg. How were you doing that?

14 DR. QUINN: Dr. Sinn and I both agreed
15 that we would use a rongeur and simply clip it at
16 the surface of the inner surface of the fossa.

17 CHAIRMAN HEFFEZ: And how many cases
18 were done with them clipped?

19 I understood -- and I may have not
20 gotten the date right -- was it February 3rd, 2000
21 that you stated to use the manufactured glenoid
22 fossa without the peg?

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1 DR. QUINN: Actually the fossa was
2 manufactured without the peg, and I believe Dr. Sinn
3 used three of them that were manufactured without
4 the peg, and then the FDA was notified. So the
5 majority of them were clipped, were actually
6 separated with a rongeur. Only three were pre-
7 manufactured without the post.

8 CHAIRMAN HEFFEZ: So in this whole study
9 we only have three cases where the peg --
10 manufactured without the peg; is that correct?

11 DR. QUINJY: That's correct.

12 Do we have the numbers up?

13 CHAIRMAN HEFFEZ: Fine.

14 DR. QUINN: Okay.

15 CHAIRMAN HEFFEZ: Okay. Dr. Runner.

16 DR. RUNNER: This is Susan Runner.

17 I just want to ask the company if you
18 could clarify. We've gone around and around about
19 the numbers here, and we keep bringing up the number
20 180 patients. It's not 180 patients. It's **168**
21 patients and 180 cases.

22 Could you clarify that? Because I think

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1 we keep rounding these numbers around, and I want to
2 be sure we're talking about the right numbers.

3 MS. VERSTYNEN: Mary Verstynen.

4 Since we had both unilateral and
5 bilateral patients enrolled into this study, we
6 found out early on that there were actually patients
7 who were enrolled for one side and later on the
8 other side was enrolled, meaning they would have
9 different surgery dates for the two sides.

10 So the cases are defined by the surgery
11 date so that we could follow the patients because
12 literally we have patients that had maybe the left
13 put in at one point and one year later have the
14 right.

15 And in order to manage the clinical data
16 and to keep the follow-ups on track, then that other
17 side later on became a second case. **As** it turns
18 out, there were **12** patients that had -- it turned
19 out in the end to be bilateral cases, but they had
20 different surgery dates for the side. So as it
21 turns out, there were **168** patients in the study
22 defined as 180 patients or 80 cases.

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1 Does that make sense?

2 There were 12 patients that had
3 different surgery dates for the two sides. If one
4 bilateral patient who had surgeries of the **sides** on
5 the same surgery data it was considered a case. So
6 it all came back to the definition -- the surgery
7 date.

8 CHAIRMAN HEFFEZ: Okay. Just for the
9 panel, I would like to also for clarification
10 understand if you can repeat to us the cement versus
11 the noncemented cases, when the cement cases were no
12 longer performed, numbers, so that it's a little
13 clear because we are throwing around different
14 numbers of two populations.

15 MS. VERSTYNEN: Right. There were 38
16 cemented cases, and I believe in the clinical report
17 it was in August of 1998, was when the last cemented
18 case was done.

19 Therefore, all of the cemented cases are
20 actually incorporated into the cohort, which are
21 three years or longer out.

22 CHAIRMAN HEFFEZ: So how many cases,

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1 noncement, have **been** followed through for three
2 years plus?

3 MS. VERSTYNEN: Eleven.

4 CHAIRMAN HEFFEZ: So the 11 cases,
5 noncement, followed for three years plus?

6 MS. VERSTYNEN: That was in the cohort,
7 yes.

8 CHAIRMAN HEFFEZ: Okay. Then the other
9 thing I want to do for the panel is I want to make
10 sure, Dr. Janosky, you feel comfortable with all of
11 your questions answered.

12 DR. JANOSKY: I was going to return
13 again to it after FDA's presentation or this
14 afternoon.

15 CHAIRMAN HEFFEZ: Okay. So if we've
16 exhausted the questions, at this point in time I'd
17 like to suggest perhaps a 15 minute break. So that
18 you understand, it's 10:15. Precisely at 10:30 we
19 will start.

20 (Laughter)

21 (Whereupon, the foregoing matter went
22 off the record at 10:15 a.m. and went

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1 back on the record at 10:30 a.m.)

2 CHAIRMAN HEFFEZ: I'll ask everybody to
3 take a seat.

4 Okay. I would like to get started.
5 Before I do get started with the **FDA** presentation, I
6 want to announce a change in the schedule.
7 Following the FDA presentation, we'll go right to
8 open committee discussion, which our primary
9 reviewers will present, and discussion.

10 We will break for lunch from 12:30 to
11 2:00 p.m. So that's a change. Lunch will be from
12 12:30 to 2:00 p.m. We will start precisely at two
13 o'clock. So I ask everybody to be back in the room
14 at two o'clock and then the rest of the schedule
15 will follow.

16 So without further ado, Dr. Susan
17 Runner.

18 DR. RUNNER: Good morning. I want to
19 thank you all for coming and deliberating on this
20 important issue this morning, and I would like to
21 start out by introducing the FDA primary review
22 team.

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1 We have Ms. Angela Blackwell, who's the
2 lead reviewer and the engineering reviewer.

3 We have Dr. Kevin Mulry, who's the
4 clinical reviewer.

5 And we have Ms. Phyllis Silverman, who's
6 the statistical reviewer.

7 Before we hear the FDA review team, I'd
8 like to sort of step back and set the stage by
9 reminding you of the importance of the history of
10 the patients in whom this device has been implanted.

11 As you all know, the term
12 "temporomandibular joint disorder" is a complicated
13 term and a collective term. It has a lot of
14 different definitions by a lot of different people,
15 and the treatment strategies range from reversible
16 therapeutic approaches to highly invasive
17 procedures.

18 There is, however, a patient population
19 for whom nonsurgical treatment is not an option, and
20 these patients have often undergone numerous
21 surgical procedures which leave them debilitated, in
22 chronic pain and with limited options.

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1 Presentation of the FDA review will
2 begin with Ms. Angela Blackwell's presentation of
3 the engineering review. Then Dr. Mulry will present
4 the clinical review and the statistical review. Ms.
5 Silverman will be available for questions on the
6 statistical section.

7 At the conclusion of **our** presentation
8 you will be able to ask FDA any questions.

9 MS. BLACKWELL: During the course of my
10 engineering review I will discuss the materials, the
11 component testing, system fatigue testing, and the
12 outstanding engineering issues.

13 The materials of the fossa component is
14 ArCom ultra high molecular weight polyethylene. The
15 materials of the mandibular component are cobalt-
16 chromium--molybdenum alloy and titanium alloy plasma
17 spray, All of these materials are commonly used in
18 orthopedics, and they all meet standards that are
19 recognized **by** FDA.

20 Component testing. There were several
21 types of component testing, including static
22 testing, pull-out testing, and push-through testing.

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1 These were all **done** to demonstrate that the device
2 was adequately -- had an adequate strength for
3 insertion and use.

4 Static testing of the mandibular
5 components. At 576 pounds, the net portion bent
6 with no breakage. This is well above the 20 to 200
7 pounds reported for bite force in **the** dental
8 literature.

9 Static test of the fossa flange. It
10 bent at **83** pounds without fracture. This was a test
11 just to make sure that the flange would take some
12 force. There's not an in vivo situation where this
13 would occur.

14 Fossa screw push-through. Eighty pounds
15 was required to push the screws through the fossa.
16 Three hundred and seventy-three pounds was required
17 to pull the screws out of bovine cortical bone.

18 The component testing indicated that the
19 device strength exceeded the insertion forces, but
20 fatigue testing is needed to more completely
21 evaluate device strength during use.

22 Fatigue testing demonstrated that all of

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1 the components working together will last for the
2 expected lifetime of the device.

3 Device failure is very common in this
4 patient population. Fatigue testing is used to
5 estimate useful life span of the device.

6 Fatigue testing of the fossa and
7 mandibular components. Cyclic compressive loading
8 for the maximum load of 145 pounds for ten million
9 cycles results with no failures in the five samples.
10 Literature estimates a non-bruxing patient would
11 load the joint with a force of between 20 and 100
12 pounds.

13 This testing was adequate to show the
14 devices will survive five to ten years under a load
15 of 145 pounds.

16 We still have one concern remaining.
17 This deals with the post removal. I think the
18 company mentioned it earlier in their presentation.
19 The original design had a post, and after I think
20 30-something patients the surgeons started removing
21 the post.

22 And then in February 2002, when the

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1 company realized that all **of** the posts were being
2 removed, they came in with a new design that didn't
3 have the post. So we asked them for additional
4 fatigue testing to address these concerns.

5 They're using the same type of testing
6 that they used before. So hopefully we'll be able
7 to compare the previous results with the fossa
8 design without a post and the fossa design with a
9 post, but with the post removed by rongeur.

10 This test is currently being conducted.
11 I believe they have four samples of each of these
12 done at this time, and they've run out with no
13 failures. So we expect the final report early next
14 month.

15 DR. MULRY: I'm going to present the FD
16 scientific review of the clinical data submitted in
17 the PMA.

18 CHAIRMAN HEFFEZ: This is Dr. Kevin --

19 DR. MULRY: Oh, I'm sorry. I'm Dr.
20 Kevin Mulry, and this is the clinical review.

21 Thank you.

22 FDA is requesting the panel's input

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1 today on this pre-market approval application, and
2 the topics I'm going to discuss are the previous TMJ
3 treatment, the device descriptions, indication for
4 use, the clinical study results, the investigational
5 sites and the investigators, adverse events, fossa
6 and bone cement, and questions for the panel.

7 In advance, many *of* these topics **have**
8 already been discussed previously by the other
9 sponsor's presentations. So what I'll do is I'm
10 going to run through just the points that I think
11 will emphasize the issues that relate to the
12 questions for the panel that we would like you to
13 address today.

14 The clinical review of the PMA involves
15 a careful consideration of all of the data presented
16 in the application. You, the panel, recommend based
17 upon the data presented whether you believe the
18 device is safe and effective for its intended uses.

19 Since there are risks associated with
20 any device, your recommendation must consider
21 whether the demonstrated benefits outweigh any known
22 or possible risks.

1 Next slide.

2 Before I begin presenting the clinical
3 data, I think it's important just to reemphasize
4 again the previous treatments that these patients
5 that are enrolled in the clinical trial have had,
6 and we look and we see approximately 70 percent of
7 them have had nonsurgical treatment. Over 60
8 percent have had disrepair. Almost 40 percent have
9 had silastic disc. We've had Proplast grafts, total
10 joint prostheses, partial joint prostheses.

11 So they've had quite a bit of treatment
12 in advance of enrolling in the study. So success
13 for these patients may be limited based upon the
14 sequelae of the multiple surgeries of the previous
15 treatments.

16 And we've already kind of gone over
17 this, and I don't think there's any need to
18 emphasize this too much, but the one point we want
19 to focus on here today is the fossa with the post
20 and just the fact that that post is the original
21 design, and that it has been used in the vast
22 majority of cases either as the post, the design

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1 picture here, or with the post removed with the
2 rongeur.

3 The other thing I'd like to emphasize of
4 it is that this is a stop device, and it's only
5 intended for total joint reconstruction and not
6 partial reconstruction.

7 You can move on. Next slide.

8 And also we have had an adequate
9 description of the mandibular condyles, the standard
10 size on the left and the narrow on the right. There
11 is, as they described, a third design, the offset
12 design, but that has not been used in the clinical
13 study to date, and I do have samples of these
14 devices which I will pass around after the
15 presentation.

16 The indications for use I think have
17 been adequately vetted. The important thing we want
18 to emphasize here is that FDA is seeking your input
19 on the applicant's proposed indications for use and
20 the data presented to support these indications, and
21 I think you've already started that discussion.

22 We can move on.

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1 I think we've had adequate discussion of
2 the primary efficacy endpoints that's on the ten
3 centimeter scale, and we're looking for the changes
4 on that VAS scale.

5 Success criteria. I'd just like to go
6 over this real quickly, although this has already
7 been discussed, that the success has two phases to
8 it. One, a patient is determined to be a success if
9 the patient has not had a permanent joint removal.

10 The second aspect is the patient has to
11 meet two of the following criteria, either a
12 reduction in pain of one centimeter on the VAS
13 scale; a reduction in interference with eating by
14 one centimeter on the **VAS** scale; or an increase in
15 maximal incisal opening of ten percent, and that's
16 all from baseline to the three-year follow-up point.

17 And the clinical study's success was
18 defined in the protocol as 60 percent or more of the
19 patients who at implantation of the device, having
20 met the above patient success criteria at three
21 years' follow-up, 60 percent.

22 We do have, as we just discussed, as

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1 Dr. Runner **did** question the sponsor regarding the
2 issue of cases and the numbers of patients, I just
3 want to reemphasize there were **180** total cases in
4 this study, but there were only **168** total patients.

5 The clinical study had the **180** cases.
6 To date we have 143 cases at the six month follow-
7 up, **89** at the one and a half years' follow-up, and
8 then we have 45 at the three-year follow-up, and the
9 sponsor is terming the three-year follow-up or the
10 45 cases as the unimputed cohort, and these are the
11 sponsor's terms, not **FDA**.

12 **FDA** views the **45** cases, which represent
13 25 percent of the total cases, as the final three-
14 year data.

15 In looking at the clinical study
16 results, we have the primary efficacy endpoints of
17 jaw pain intensity, interference with eating, and
18 maximal incisal opening. I'd like to shift to the
19 right-hand side of the slide where we have the
20 cohort of 45 that were evaluated at the three-year
21 follow-up visit, and what we're looking at here is
22 the difference between visit one pre-operative, and

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visit eight three-year follow-up visit

3 The difference in the change in the jaw
4 pain intensity was approximately 5.7 centimeters on
5 the VAS scale. The interference with eating **was**
6 approximately 5.8 centimeters, and the maximal
7 incisal opening, we see an increase of about 10.27
8 millimeters.

9 We're not going to discuss the imputed
10 cohort at this time because we feel that the 45
11 patients that were actually evaluated at the three-
12 year follow-up are the data that we think is the
13 more relevant data.

14 The T test analysis that was done on
15 this data shows that in the total group there was a
16 statistical difference in all three primary
17 endpoints between baseline and assessments at all
18 time points from one month follow-up to three years'
19 follow-up.

20 And for jaw pain intensity and
21 interference with eating, over **80** percent of the
22 improvement was experienced by six months with the
23 maximum incisal opening approximately 97 percent of

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1 their overall effect of improvement occurred by six
2 months.

3 So generally, the results plateaued
4 around six months, and from there on **we** didn't see
5 much change in the results or the outcomes. So the
6 question for the panel **is** whether the results for
7 jaw pain intensity, interference with eating, and
8 maximal incisal opening for the cases with three-
9 year data which represent **25** percent of the
10 implanted population adequately represent the
11 expected outcomes for the total study group of three
12 years.

13 One clinical study, as **Dr.** Quinn has
14 presented already, was conducted to support this
15 pre-market approval application, and the thing I
16 want to emphasize here again is that we look at the
17 fact that **132** of the **180** cases were treated at site
18 one and 40 at site two, and the remaining eight were
19 at the other three remaining site.

20 A multivariate analysis noted a
21 significant interaction between time and
22 investigational site with jaw pain intensity at site

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1 one. The cases began with a much higher VAS score
2 of about nine centimeters versus approximately 5.63
3 at the other sites combined and also experienced a
4 relatively larger amount of improvement over time
5 compared to the other sites.

6 So the question for the panel is whether
7 the fact that **96** percent or **172 of the 180** cases
8 were treated at only two sites. Does this present a
9 potential for bias in the clinical outcomes?

10 Next slide.

11 **As** far as adverse events go, actually it
12 should be 51 of the 168 or approximately 30 percent
13 of the patients have reports of adverse events, and
14 I think Dr. Quinn has adequately described that **most**
15 of these adverse events related to excision of
16 tissue, either the neuroma or heterotopic bone,
17 facial trauma, motor vehicle accidents,
18 coronoidectomy or ear problems, ear infections.

19 Eight patients required permanent device
20 removal, and two of those were fossa components due
21 to necrosis, infection, and swelling; five total
22 joints due to pain, swelling, infection, and

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1 ankylosis; and one mandibular component due to
2 dislocation.

3 I think it's most important to note,
4 however, that 117 of the 168 or approximately 70
5 percent had no adverse events at all.

6 Now, the 30 percent adverse event rate
7 may appear to be high. However, I think it's
8 important to emphasize that most of these adverse
9 events resolved themselves, did not required device
10 removal, and met the success criteria.

11 The issue for the panel is to discuss
12 the rate of adverse events in this patient
13 population.

14 I just wanted to emphasize here that the
15 purpose of the post on the fossa was to facilitate
16 retention of bone cement, and as I think we just
17 discussed prior to the break, the use of bone cement
18 was discontinued in August of 1998, and of the 180
19 cases, 38 or 21 percent had bone cement used and 142
20 or 79 percent did not.

21 And the issue for the panel here is that
22 the company plans to market the device as a

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1 noncemented fossa or as a cemented fossa. In the
2 clinical data set, some of the cases are with cement
3 and some cases are without cement, and the panel
4 needs to discuss the data in light of these two
5 different methods.

6 In summary, the results of the analysis
7 of the primary efficacy endpoints demonstrate that
8 approximately 98 percent or 44 out of the 45 cases
9 were successes well beyond the 60 percent which was
10 the definition of success in the protocol. The
11 success criteria for jaw pain intensity and
12 interference with eating was one centimeter.
13 However, the improvement of approximately five
14 centimeters was well beyond the success criteria,
15 and for the maximal incisal opening the improvement
16 was beyond the ten percent needed for success.

17 Patient satisfaction was over 90 percent
18 of all visits up to three years. **As** previously
19 noted the patients enrolled in this clinical trial
20 were selected only after nonsurgical treatment had
21 failed or after a previous implant failure and also
22 after a history of an average of 5.2 previous

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1 surgeries of the TMJ area.

2 Success of the surgical results from
3 this reconstruction must often be tempered by the
4 realization that reduction in painful symptoms and
5 increase in function may be limited at best. To
6 date the clinical study results had exceeded the
7 criteria for success.

8 As I noted at the beginning of this
9 presentation, we are seeking **your** input today on the
10 applicant's proposed indications for use and the
11 data presented to support these indications, and
12 what I'd like to do is just run through the
13 questions that we would like the panel to address
14 today.

15 Question one, can the results for jaw
16 pain intensity, interference with eating, and
17 maximal incisal opening for the cases presented with
18 three-year data which represent 25 percent of the
19 implanted population adequately represent the
20 expected outcomes for the total study group at three
21 years?

22 Question two, **132** of the 180 cases were

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1 treated at site one, Dr. Quinn. Forty of the 180
2 cases were treated at site two, Dr. Sinn. Eight of
3 the 180 cases were treated at sites three, four, and
4 five combined. Does the fact that 96 percent or 172
5 of the 180 cases -- the fact that they were treated
6 at only two sites present a potential for bias in
7 the clinical outcomes?

8 Question three, 51 of the 168 implanted
9 patients have reports of adverse events. Of these
10 51 patients, eight required permanent device
11 removal, Please discuss the rate of adverse events
12 in this patient population.

13 Number four, the company plans to market
14 the device as a noncemented fossa or as a cemented
15 fossa. In the clinical data set, some of the cases
16 are with cement and some cases are without cement.
17 Please discuss the data in light of these two
18 different methods.

19 Question five, the sponsor has provided
20 engineering test data and a protocol for testing on
21 both the new fossa design without a post and the
22 fossa with a post removed using the rongeur. Do the

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1 engineering test data and protocol as presented give
2 adequate safety and effectiveness information on
3 this device?

4 And the last question, (a) FDA has
5 reviewed proposed labeling. Please discuss the
6 draft labeling as presented.

7 (b) Please discuss the need for
8 training and the type of training protocol that may
9 be necessary for safe and effective use of this
10 device.

11 (c) The sponsor intends to complete the
12 pivotal PMA study following all patients for three
13 years. Please discuss the need for any additional
14 post market studies and issues that should be
15 addressed were those studies to be required.

16 Thank you for the opportunity to
17 present, and Ms. Blackwell and I will be happy to
18 answer any questions you might have.

19 CHAIRMAN HEFFEZ: Dr. Patters.

20 DR. PATTERS: Mark Patters.

21 I have a question actually for Ms.
22 Silverman if that would be all right.

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1 CHAIRMAN HEFFEZ: Sure.

2 DR. PATTERS: Does FDA have an opinion
3 on the definition of a case and how that definition
4 was applied to these studies as a case being a
5 surgical procedure, whether it be replacement of one
6 joint or both joints, and that replacement of both
7 joints at two different times would be two cases?
8 Do you have an opinion on that?

9 MS. SILVERMAN: That is not a
10 statistical question.

11 Phyllis Silverman.

12 That is a clinical question. That
13 really isn't a statistical question.

14 DR. PATTERS: Well, how does one handle
15 the statistics when some individuals have a single
16 surgical procedure as defined as a case and some
17 individuals have two surgical procedures defined as
18 a case such that there is twice the likelihood of
19 failure in someone who's had two procedures even if
20 done at the same time than someone who has done one
21 procedure?

22 MS. SILVERMAN: Right. In this data set

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1 the people that were considered two cases, the 12
2 patients that were considered two individual cases,
3 I believe they were treated as if they were
4 independent cases, and because it was such a small
5 percent of the total population, I didn't make an
6 issue out of it.

7 Generally if you **would** have **bilateral**
8 cases, then you would have to account for within
9 patient correlation. You'd have to do slightly
10 different statistics, but in this data analysis I
11 let them treat it as individual cases.

12 DR. PATTERS: Thank you.

13 DR. JANOSKY: Ms. Silverman, I was
14 hoping to catch you before you walked away. **So**
15 would you mind? I want to follow in that vein, but
16 I want to take a little bit further.

17 CHAIRMAN HEFFEZ: Dr. Janosky.

18 DR. JANOSKY: Janine Janosky. Sorry.

19 If I take a look at the plots that the
20 sponsors have provided and I look at the three
21 baseline data points and they're graphed, I can tell
22 by looking at those graphs at baseline that those

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1 are **not** symmetrical distributions.

2 Given that point of information, the
3 second point of information is there's a controversy
4 in statistics as to whether Likert type VAS scales
5 should be analyzed as parametric or nonparametric
6 techniques.

7 Taking those two points together and
8 also adding the third point that was just discussed
9 about data being dependent and treating as
10 independent, were there other types of analyses that
11 were done that would have taken into account all
12 three of these issues?

13 MS. SILVERMAN: Well, they could have
14 done a nonparametric analysis to show how it
15 compared to the parametric, but I did not request
16 that. They did a repeated measures analysis, and I
17 thought that that would account for like some within
18 patient variability and stuff, but I did not request
19 any other analyses.

20 DR. JANOSKY: That **was** your decision?
21 That was the sponsor's decision? How was that
22 decision made?

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1 MS. SILVERMAN: Well, the sponsor
2 chooses what kind of analyses they wanted to do, and
3 we can request additional analysis if we thought
4 that they were necessary, but when I looked at the
5 overall picture I thought it was pretty dramatic,
6 that the effect was pretty dramatic, and I did not
7 ask them to do a different kind of analyses.

8 DR. JANOSKY: So given the analyses that
9 were done, did the sponsor provide any information
10 to show that the statistical assumptions were meant
11 for those particular techniques?

12 MS. SILVERMAN: I don't believe they
13 did.

14 DR. JANOSKY: Thank you.

15 CHAIRMAN HEFFEZ: Any other questions?

16 Dr. Li.

17 DR. LI: Steve Li.

18 A question for I think it's probably
19 Angela on the mechanical testing.

20 There was a fatigue test where the fossa
21 and mandibular component was placed in fatigue.

22 MS. BLACKWELL: Yes, there were several.

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1 DR. LI: Right, and the conclusion, I
2 think, on those was that there was no failure of the
3 components.

4 MS. BLACKWELL: Yes.

5 DR. LI: So my question is: what was the
6 failure criteria for the fossa component?

7 MS. BLACKWELL: What **was** the failure
8 criteria?

9 DR. LI: In other words, how would you
10 know? What would have counted as a failure for the
11 fossa? Did it have to break?

12 MS. BLACKWELL: Breakage, fracture.

13 DR. LI: So if there was severe wear or
14 deformation, would that have counted as a failure
15 criteria?

16 MS. BLACKWELL: I believe so.

17 DR. LI: So at these loads, there was no
18 deformation and no wear in the fatigue tests?

19 MS. BLACKWELL: They didn't do
20 microscopic level analysis. So you couldn't get a
21 definite answer on that from the test protocol.

22 DR. RUNNER: I think maybe the specifics

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1 of the test protocol might be better answered by the
2 sponsor in terms of --

3 DR. LI: Okay. That would be a whole --
4 I'm sorry. I didn't mean to --

5 MS. BLACKWELL: Yes. **Well, also** bear in
6 mind that the gentleman who's here today, he didn't
7 do the tests that we're talking about. It was done
8 like eight years ago or something.

9 DR. LI: Well, my general question is
10 you're doing a test and then saying the components
11 pass, but I don't know what the pass-failure
12 criteria is other than frank breakage.

13 DR. RUNNER: Angela, I think you should
14 have the company answer that question.

15 MS. BLACKWELL: Yeah.

16 MR. ROMAN: Shawn Roman.

17 The acceptance criteria, there are two
18 things looked at for the fossa compliance. As
19 Angela mentioned, they are looking for a fracture or
20 breakage of the fossa component, and also on a
21 macroscopic level looked at where on the fossa
22 component, you know, and on the articular surface.

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1 DR. LI: That was just a visual surface
2 is there wear or is there not wear.

3 MR. ROMAN: That's correct.

4 DR. LI: How about deformation?

5 MR. ROMAN: Yeah. During the visual
6 inspection of the fossa component?

7 DR. LI: So there was no indentation of
8 the metal into the plastic after this test?

9 MR. ROMAN: No, sir.

10 DR. LI: Do you find that a little
11 unusual, given that you have a high load, small
12 area, millions of cycles, that there is no
13 indentation?

14 MR. ROMAN: Given the large surface
15 contact between the mandibular component and th
16 fossa component, I would say no.

17 DR. LI: Because even in a total HEP, we
18 just got a much larger surface area. There's
19 definite deformation under these similar conditions.
20 So if there is no wear and no deformation, one I
21 think is the follow-up question to somebody else.
22 The load may be going somewhere else, right?

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1 Because certainly there's enough load in there that
2 should cause wear or deformation on the polyethylene
3 was exactly mechanically appropriate.

4 So one question would be a closer
5 examination of the materials of construction and how
6 the implants are fixed and just exactly where is the
7 load going.

8 MR. ROMAN: The point was brought up
9 that that is something that we can take a look at
10 now because we are currently running fatigue testing
11 to address the issues between removed fossa posts
12 and posts that are -- or I'm sorry -- fossa
13 components that were manufactured without the posts.

14 DR. LI: Okay. Obviously my concern is
15 you're undergoing another set of tests to test a
16 component without the post, but I can't see how it
17 would help but pass under the current conditions of
18 the test.

19 MR. ROMAN: Okay.

20 DR. LI: So under those conditions, I'm
21 not even sure why you would particularly run that
22 test if there's really no way for the polyethylene

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1 to fail, if you see what I mean.

2 DR. ANSETH: Kristi Anseth.

3 And just one quick follow-up. So in the
4 studies that you're undergoing right now with the
5 non-post fossa, there will be no other further
6 analysis, the wear or anything other than
7 macroscopic.

8 MR. ROMAN: That's something that we
9 can. We can include a more microscopic analysis of
10 the fossa bone that's deemed necessary.

11 CHAIRMAN HEFFEZ: Dr. Li?

12 R. LI: I'm sorry. I'm back to one one
13 last -- I'm on the fixation issue. I think the test
14 you did was, if I remember right, was a screw pull-
15 through. You tried to basically measure the amount
16 of force it took to pull the screw through the hole,
17 which obviously was described as not really an in
18 vivo number, would not have been a much more useful
19 number to essentially apply a small load. **So** you
20 cycle the plastic in and out of the screw and see
21 how long it takes actually to pull the screw that
22 way, that way through because that's the way it's

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1 going to fail. It's not going to rip out in one
2 giant pull, but it probably will loosen if you apply
3 kind of an in and out motion along the axis of the
4 screw,

5 MR. ROMAN: It's my understanding though
6 the fossa component does not see a cyclical load in
7 the sheer direction. So --

8 DR. LI: Well, I'm sorry. Pick it in
9 the other direction. I mean it doesn't really
10 matter in what direction. I think it's going to
11 move.

12 MR. ROMAN: In the other direction, you
13 would have this over the temporal bone, keeping that
14 micro motion from occurring.

15 DR. LI: So it's fully supported on the
16 superior?

17 MR. ROMAN: Yes.

18 DR. LI: Okay. I didn't catch that on
19 the drawing.

20 CHAIRMAN HEFFEZ: Ms. Helms.

21 MS. HELMS: Thank you.

22 Liz Helms.

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1 **My** follow-up. On the 12 patients that
2 went from unilateral surgery to bilateral surgery,
3 of those 12 patients was there cause from the load
4 going somewhere else, or was that a condition that
5 was present and needed to have treatment and you
6 decided to wait on that? What were the
7 circumstances of those 12? Either, either?

8 DR. QUINN: Yeah. Patients who had
9 initially one --

10 CHAIRMAN HEFFEZ: Dr. Quinn.

11 DR. QUINN: I'm sorry. Dr. Quinn.

12 You asked the patients who initially had
13 one side place and then had a sepsis contralateral
14 side?

15 MS. HELMS: Right.

16 DR. QUINN: Okay, and what was the
17 question about?

18 MS. HELMS: Okay. The question was what
19 was the cause of those other 12 to come back and
20 have the other side done.

21 DR. QUINN: I'm not sure what was the
22 cause. Usually the two reasons patients get

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1 prosthetic plates are usually mechanical
2 difficulties. It's relatively easy to make the
3 decision when they are fused, but when it's pain,
4 since it's so subjective, normally patients are
5 largely the decision maker as to what side might be.

6 We ask them in terms of their pain if
7 the pain level is a nine out of ten, but it's 90
8 percent left sided and they're functioning **on the**
9 contralateral side, we will replace the one joint.

10 I think the issue that Dr. Janosky
11 raised about how do they play into the statistics,
12 and I'm not a statistician, but it's difficult for
13 us to follow them when they're bilateral joints
14 unless we separate them clearly because they'll
15 come in and say they have pain, and we have to side
16 that pain, So that is one of the reasons we did
17 separate it out.

18 The major reason for coming back
19 hopefully in this study was that was that they were
20 pleased enough with the results in the reduction of
21 pain and the increase in function on the first set
22 that they requested the second.

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1 The only other reason it would be is --
2 and I can't speak to this with all of these patients
3 in mind -- at the time of surgery because this **is**
4 not a knee; it is one bone with both joints in
5 there. It is sometimes difficult for us to
6 determine which side is actually causing the
7 ankylosis. We could have radiographic evidence **of**
8 fibrous or bony ankylosis, but it's sometimes
9 difficult.

10 There are times that we get permission
11 to replace both joints. We will go into the worst
12 joint radiographically and pain-wise and sometimes
13 stop because if we do achieve 30 to 33 millimeters
14 with replacing one joint, it will stop. Because if
15 we do achieve 30 to 33 millimeters with replacing
16 one joint, we will stop.

17 It is the pain issue that I think
18 largely drives the second side being done and
19 patients will say, "Now this one is bothering me,
20 and I want the same result that we got from the
21 first side."

22 CHAIRMAN HEFFEZ: I think her specific

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1 **question** was **she** wants to know whether the surgery
2 on one side caused deterioration on the
3 contralateral side; is that correct?

4 MS. HELMS: Right. Do you know if any
5 of those 12 was there a shift in the load **to** the
6 opposite side where the patient originally had not
7 presented with a problem to the opposite **side**. So
8 there was just a decision to go ahead and **do** a
9 unilateral implant rather than a bilateral implant.

10 Was a load shifted to the other side
11 after the implant was done that created degeneration
12 in that other joint?

13 DR. QUINN: That's a good question. I
14 don't know of any way of measuring that. The
15 attempts to measure intra-articular loads have been
16 less than optimal. I'm not sure how you can measure
17 that.

18 But if patients have a progressive
19 degenerative disease as osteoarthritis, it is
20 potential that they could continue that degeneration
21 of the non-implanted side, and I think that's the
22 most common we implant the second side.

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1 CHAIRMAN HEFFEZ: Thank you.

2 Dr. Janosky.

3 DR. JANOSKY: The question is for Dr
4 Mulry and Ms. Silverman.

5 I want to return to the question that I
6 raised to the sponsor this morning, if we could
7 address it together a little. On your slide you
8 have clinical study cases, and let's just use case
9 to be whatever they're defining case to be
10 irrespective of whether that side or not, just to
11 deal with the issue for a second more
12 simplistically.

13 Their primary endpoint was three years.

14 DR. MULRY: Yes.

15 DR. JANOSKY: For the study, and based
16 on what you had presented in the slide and based on
17 what I have gathered from the information, they had
18 presented is that out of 180 cases at year three,
19 you had 45 cases.

20 DR. MULRY: That's correct.

21 DR. JANOSKY: To which you had complete
22 data.

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1 DR. MULRY: That's correct.

2 DR. JANOSKY: Which given the issue that
3 I was talking about this morning in calculating
4 follow-up, you calculated that there would be a 25
5 percent follow-up.

6 DR. MULRY: That's correct.

7 DR. JANOSKY: Now, one of the questions
8 I asked the sponsor this morning was: out of those
9 45 cases, what number came from Dr. Sinn and what
10 number came from Dr. Quinn. Do you have that piece
11 of information for us?

12 DR. MULRY: No, I don't believe we do.

13 MS. SILVERMAN: I do know that all 45
14 were at those two sites, but I don't recall what --
15 you know, I might have that.

16 DR. JANOSKY: Because it would be
17 reasonable for me to think it was a 70-30 split like
18 there was in the patient recruitment, but that might
19 be unfair to just come to that conclusion.

20 DR. MULRY: Mary, would you have that?

21 DR. JANOSKY: Was the sponsor able to
22 get that piece of information?

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1 It is exactly 70-30. Okay.

2 While they're just confirming that, let
3 me raise one other issue with you. Maybe you can
4 enlighten me a little bit. I see the two
5 instruments are paper and pencil, and one instrument
6 of the outcomes is face to face. The patient needs
7 to be there.

8 The sponsor gave the discussion that
9 perhaps they didn't have complete data for all of
10 those follow-up because either the patients were
11 doing well so that it didn't come back or
12 geographically they were at such a distance they
13 didn't want to make the trip, et cetera, et cetera,
14 et cetera.

15 If I go with that second hypothesis that
16 they had postulated, which was the patients are at
17 such a distance they didn't want to come back,
18 confirming that hypothesis for me would be that they
19 would at least have two of those assessments done
20 per patient. In that they would have said, "Okay.
21 You're not willing to come back, but will you please
22 complete these VAS for us because those are patient

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1 self-report?"

2 Do you have any indication that that was
3 done, that they have missing data depending on type
4 of outcome?

5 DR. MULRY: I don't think there was
6 enough information in the application to tell us one
7 way or the other whether they did that.

8 DR. JANOSKY: Okay. So it's *not* fair
9 for me to necessarily conclude that that second
10 hypothesis, which was geography, was one of the
11 issues that patients didn't return? Because that's
12 a very simple thing to do, ask a patient to complete
13 paper and pencil.

14 DR. MULRY: I don't think there's enough
15 information in there for us to make that
16 determination. We really have to depend on the
17 sponsor to let you know what they actually did in a
18 collection of data.

19 DR. JANOSKY: Based on your experience
20 with these types of studies, would you expect to see
21 those types of data?

22 DR. RUNNER: I think with our experience

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1 we ask sponsors to get data in any way they can to
2 follow patients.

3 DR. JANOSKY: Based on my experience I
4 have the same experience, whether that means partial
5 records or not partial records.

6 Does the sponsor have -- is it a 70-30
7 split for that n equals 45 at three years?

8 We're still searching. Okay. I'll wait
9 a while longer then. Thank you.

10 DR. JANOSKY: I'd like to follow up with
11 that question and ask the 11 patients that were
12 treated with noncemented. What was the distribution
13 as well?

14 Are there any other questions from the
15 panel? Ms. Howe.

16 MS. HOWE: Elizabeth Howe.

17 Dr. Mulry, my question has to do with
18 your question to us, 6(b), about training. Was
19 there any material given to you to review regarding
20 proposed training that would go along with this
21 product?

22 DR. MULRY: Not in the clinical section,

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1 no.

2 MS. HOWE: Is there anything available
3 from the sponsor that would show an intent to do a
4 training component?

5 MS. BLACKWELL: We were told that they
6 were planning to have training for everyone before
7 they were allowed to place the device, **and** I believe
8 a video was made, but we haven't seen it yet. We
9 usually do labeling and real detailed work after the
10 panel meeting simply because of the time issue.

11 MS. HOWE: Thank you.

12 CHAIRMAN HEFFEZ: Mr. Mulry, I have a
13 question for you. In reviewing the indications,
14 many times the patients had multiple diagnoses. Was
15 any attempt made to your knowledge to find a primary
16 diagnosis so that it could be a little bit clearer
17 what the indications were for this surgery?

18 DR. MULRY: Not that I'm aware of.

19 CHAIRMAN HEFFEZ: I'll ask the sponsor
20 if they made an attempt to find a primary diagnosis.
21 I'll address it to Dr. Quinn.

22 For example, some of them have traumatic

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1 arthritis, deformity, and several diagnoses, and
2 they're all tallied as that. Is there one table
3 that can tell us what a primary diagnosis is because
4 clearly many of those have secondary diagnoses.

5 DR. QUINN: Well, we didn't make an
6 attempt to identify one as primary. I'm not sure of
7 the multivariate analysis, whether they were broken.
8 My knowledge is that they weren't. We didn't list
9 one as the primary.

10 Mary, do we have the data that Dr.
11 Janosky is requesting?

12 MS. VERSTYNEN: Mary Verstynen.

13 I have the data for the cohort imputed
14 group of 59 where 41 of the 59, which is 70 percent,
15 were Dr. Quinn's and 18, which is 31 or 30 percent,
16 for Dr. Sinn. So it was a 70-30 split, and there's
17 no reason to believe that it wasn't the same for the
18 45 number.

19 CHAIRMAN HEFFEZ: How about the 11, the
20 cemented 11? Do you know what the distribution is?

21 MS. VERSTYNEN: It would obviously be
22 more of Dr. Quinn's because Dr. Quinn had 31 of the

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1 38 and Dr. Sinn only cemented seven cases, but I
2 don't know exactly of the 11 how many were Dr.
3 Quinn's and how many were Dr. Sinn's.

4 CHAIRMAN HEFFEZ: And as far **as** -- while
5 you're up there, as far as the diagnosis
6 distribution, is that data available to be able to
7 break it down into primary diagnosis?

8 MS. VERSTYNEN: No. I remember
9 discussing this early on in the protocol, and it
10 seemed to be very difficult to put a primary
11 diagnosis on these patients because of the multiple
12 diagnosis that most of them had. So there's no way
13 to go back and collect it unless we ask for it
14 retrospectively.

15 CHAIRMAN HEFFEZ: And for the panel, can
16 you define traumatic arthritis, and could you define
17 aseptic necrosis?

18 MS. VERSTYNEN: I think I'll defer to a
19 clinician on that one.

20 CHAIRMAN HEFFEZ: Okay.

21 DR. QUINN: I think the difficulty of
22 the diagnosis question in general is that the

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1 patient presents with signs of late stage
2 degeneration and anky osis. Which one is primary
3 and which one is secondary?

4 We defined traumatic arthritis as when
5 there was in the preoperative form an identifiable
6 event, when the patient said, "On February 11th,
7 2000, I was in a motor vehicle accident with direct
8 facial trauma. Prior to that I had no symptoms."

9 Then we labeled the degenerative changes
10 as traumatic osteoarthritis as opposed. So it's
11 purely labeling by history.

12 CHAIRMAN HEFFEZ: **And** aseptic necrosis,
13 how did you define that?

14 DR. QUINN: Well, aseptic necrosis and
15 avascular necrosis, as you know, is a hot topic in
16 the temporomandibular joint literature. If there
17 was imaging evidence where avascular necrosis was
18 mentioned as part of the imaging, I'm not a believer
19 that the avascular necrosis is as prevalent in the
20 temporomandibular joint as in other joints, but if
21 the imaging prior to surgery mentioned avascular
22 necrosis or aseptic necrosis, we use the term based

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1 on the radiologic evidence.

2 CHAIRMAN HEFFEZ: So it was based on the
3 radiologist's diagnosis?

4 DR. QUINN: Yes.

5 CHAIRMAN HEFFEZ: Okay. Excuse me. Dr.
6 Bertrand.

DR. BERTRAND: Peter Bertrand, a
8 question for Dr. Mulry.

9 You've charged us with understanding
10 whether or not the three-year data is reflective of
11 the rest of the patient group.

12 DR. MULRY: Yes, sir.

13 DR. BERTRAND: That may very well be
14 true at three years with the others for pain,
15 chewing ability, and incisal opening. My concern
16 though is how is the three-year implant arrived at.
17 Why not six years? And why that three years may not
18 be sufficient time to see any type of immune
19 reactions manifested in the patient group.

20 DR. RUNNER: I think -- this is Susan
21 Runner -- I'm going to answer that question. We
22 developed a guidance document with input from

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1 clinicians some years ago that stated that for
2 temporomandibular joint implants there would be a
3 three-year cutoff for data. That was arrived at
4 with input from the various people.

5 Obviously you could continue out
6 patients for a long period of time to get additional
7 data, but that has been the standard.

8 It has also been a primary standard in
9 orthopedic studies as well.

10 DR. BERTRAND: I'm going to expose my
11 immunologic ignorance here, but for my own
12 edification maybe anybody can help me understand it.
13 Is three years sufficient time to explore the
14 possibility of immune functions, especially if
15 there's some material failure at four, five, six,
16 and seven years?

17 I don't know if anybody can shed any
18 light on that.

19 CHAIRMAN HEFFEZ: Dr. Li.

20 DR. LI: Well, I can give an answer from
21 a total knee side that three years would be an
22 extraordinarily short time to see any immune

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1 response to polyethylene or metal debris. The wear
2 rate would have to be horrendous for it to show up
3 in three years.

4 But a bad or high wear rate would
5 probably take a minimum of five to seven years
6 before you saw the immunological response. So if
7 you had -- so unless the wear rate was horrendous,
8 which does not appear to be in this case, the wear
9 rate still could be high enough to cause a response
10 at five, which would be invisible at three if it was
11 a total hip or a knee.

12 DR. BERTRAND: So a question for Susan
13 Runner then. Was there consultation with people
14 concerning reactions where a three-year time frame
15 was developed?

16 DR. RUNNER: I don't believe that's the
17 case.

18 DR. BERTRAND: Thank you.

19 CHAIRMAN HEFFEZ: Dr. Suzuki.

20 DR. SUZUKI: Jon Suzuki.

21 A question for Dr. Mulry really. With
22 respect to the determining what the learning curve

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1 is on implanting these devices, is there a way that
2 the panel can look at either the rate at which the
3 devices had to be removed or the morbidity that
4 occurred as the surgeon gave experience?

5 The reason I'm asking this question
6 about the learning curve is that it may impact on
7 answering like training issues and whether or not
8 these two sites are acceptable.

9 DR. MULRY: I think all of those could
10 be factored in. I think it would be helpful if we
11 heard maybe from Dr. Quinn who has been training the
12 other surgeons for this technique as to what value
13 it's had and what they've had to do in the process
14 of training, along with the other information.

15 DR. QUINN: I think it's an excellent
16 point. I don't think we saw any glaring differences
17 based on the curve, but I think Dr. Sinn and I would
18 be considered relatively experienced surgeons.

19 I think it is an issue, and I think it's
20 not only an issue in this device, but if you look at
21 the leap frog initiatives in this country that
22 they're looking at a minimum number of procedures in

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1 a lot of things like open heart surgery and
2 angioplasties, and so I would apply the same logic
3 to this device, that hopefully it will be done by
4 surgeons and centers where there's a minimum amount
5 that would determine that expertise.

6 I don't know what that is. Remember
7 we're starting with a small number, to begin with,
8 and I think we have to keep that in consideration.
9 Our plan is to have any surgeon who is going to
10 implant this device train by either Dr. Sinn or
11 myself and then move to a train the trainer mode.

12 They would also have to take a course,
13 and that's part of the videotape that's being
14 developed. I feel very strongly that someone who
15 has no background in this surgery shouldn't make the
16 hyper leap into placing a total joint prosthesis,
17 but I think you can use the same logic in any
18 advanced reconstructive procedure in the orthopedic
19 world as well.

20 CHAIRMAN HEFFEZ: Okay and we'll just
21 have two additional questions. Ms Helms and then
22 Dr. Burton, and then we'll move on to the reviewers.

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1 MS. HELMS: Thank you.

2 Elizabeth Helms.

3 I have a question for Dr. Quinn on
4 number three and a question for Dr. Mulry on number
5 six.

6 Of the 52 patients that had the adverse
7 effects, do you know what their quality of life is
8 to date? And were any of those 52 incorporated into
9 the end of the three-year trial in that information
10 of the outcomes?

11 DR. QUINN: I think the pat. key that
12 identifies every patient and also identifies the
13 adverse events, I could link them to them. I'm not
14 sure I could give you a comprehensive listing.

15 When you say quality of life in terms of
16 the parameters we followed or something beyond that?

17 MS. HELMS: Right. The pain, for one.

18 DR. QUINN: Well, actually we could link
19 the adverse events to specific patients and look at
20 the data. I'm not sure I could recite it for you.

21 DR. RUNNER: Well, excuse me, but didn't
22 all 52, except for the eight removed, didn't they go

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1 on to resolve their adverse events and become
2 successes?

3 DR. QUINN: Except for the eight, yes.

4 MS. HELMS: Except for the eight.

5 Right, okay.

6 DR. QUINN: And what was the second part
7 of the question?

8 MS. HELMS: The second part of the
9 question is number six. On the labeling, the
10 disclosure information, is there significant
11 disclosure information in the labeling for consumers
12 to understand what is being implanted?

13 DR. RUNNER: Susan Runner.

14 The company has provided the patient
15 labeling, and that has been reviewed by our Office
16 of Health Industry Programs, and it's inconsistent
17 with other TMJ implant patient labeling materials.

18 CHAIRMAN HEFFEZ: Okay. Dr. Burton.

19 DR. BURTON: Richard Burton, and this
20 could either go to Dr. Mulry or to Dr. Quinn.

21 One thing, we've talked about some wear
22 issues, and they've talked about whether fatigue

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1 testing and how long it would last and things, but
2 has anyone at least even -- I always say this,
3 "venture to guess" -- but what is the expected life
4 expectancy that you informed the patient of?

5 I looked at the patient literature, and
6 it doesn't really address that, and obviously you're
7 dealing if you're looking at the demographics with
8 a reasonably young population. You know, if you
9 have a device that can last whether it's five years
10 or ten years or 15 years and you have a 30 year old
11 patient, and these are multiply operated patients,
12 what then is the future that they're looking at as
13 well?

14 And I mean, I think that the patient
15 needs to at least I don't know whether it's publish
16 or not, but it needs to at least have some concept
17 of: fine, I'm 30 years old. I'm getting this joint
18 implant. Hopefully this will improve my pain and
19 function, but what is my long-term expectancy with
20 this?

21 I know what we tell patients and knowing
22 some orthopedic colleagues what they tell them. You

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1 know, if you're X years old and you get a knee done,
2 you know, this is what you can reasonably expect.
3 This is what you can expect from your hip. What can
4 I expect from this implant in terms of a life
5 expectancy?

6 And obviously there is a range, and at
7 this juncture obviously given the time frame out,
8 somewhat obviously speculative.

9 DR. MULRY: Yeah, I'm not sure I can
10 answer that from looking at the clinical data
11 because the data is only out to six years, and I
12 think that was five patients. So we really don't
13 have anything beyond that to draw upon in terms of
14 data.

15 So maybe Dr. Quinn or one of the
16 engineers may be able to answer that.

17 DR. QUINN: It's an excellent question
18 because every patient who has this asks me that
19 question, and in honesty you have to say, "I can
20 only tell you the longest one out is six years and
21 one month."

22 I'm not sure there is a method, and if

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2 the statistician could help me to say if 59 of them
3 are out four years, I can impute that they would
4 last a range. I don't know whether you can do that,
5 but my experience with the most recent stock implant
6 that we used in over a period of 12 years, implanted
7 a good number of them, the average life span was
8 about six and a half years where we started to see -
9 - but we saw significant, to get to Dr. Li's point,
10 polymeric debris where the current episodic
11 swelling, loosening much earlier in the use of that
12 device.

13 And I may have to defer to Dr. Runner,
14 but my understanding was in 1994 during this initial
15 submission, there was a definition that five years
16 was a reasonable expectation from the
17 temporomandibular joint device. I think that was
18 the arbitrary definition at the beginning of this
19 process, and if anyone can comment beyond that, I
20 would appreciate it.

21 DR. RUNNER: I believe that was the --

22 CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: I'm sorry.

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1 I believe that was the idea behind the
2 ten million cycles with an estimate of two mil ion
3 cycles per year as an estimate. I believe that's
4 what went into that number for the fatigue testing.

5 DR. QUINN: I think the variability here
6 is, as you know, that I thought the latest wear
7 testing I saw was in the normal adult joint you
8 would have 13 million functioning rotations in a
9 ten-year period.

10 The problem is that variability in this
11 case because in the normal patient, your teeth are
12 in contact 18 to 24 hours a day, and a bruxer can be
13 up to four hours. So I think there's a huge
14 variability in there.

15 CHAIRMAN HEFFEZ: One of the problems,
16 you say in six years the other type of prosthesis
17 demonstrated metallosis and problems, and yet we
18 didn't study very well the microscopic debris here,
19 and we're not at six years with this device. So I
20 think you have to just fill in and paint the picture
21 a little bit better.

22 DR. QUINN: Well, I'm comparing a device

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1 that largely had a methyl methacrylate head, and
2 wear testing is grossly different than a cobalt
3 chrome head against polyethylene. So I think
4 that -- is that the point?

5 CHAIRMAN HEFFEZ: Well, it goes back to
6 Dr. Li's point where how much of the testing has
7 been done from a microscopic point of view to
8 demonstrate the wear.

9 DR. QUINN: I should mention that we did
10 do testing against what we referred to as the
11 predicate device as part of the submission, and we
12 did use five of the devices that I was referring to
13 and compared them, and we do have that data if it
14 would be helpful.

15 CHAIRMAN HEFFEZ: This data would be
16 representing five in vitro testing?

17 DR. QUINN: I may ask Shawn to help me.
18 We did test the Lorenz TMJ device
19 against what we referred to as the predicate device.

20 CHAIRMAN HEFFEZ: We can't --

21 DR. RUNNER: I think for PMAs, PMAs have
22 to stand on their own.

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1 CHAIRMAN HEFFEZ: Right.

2 DR. RUNNER: We don't really compare to
3 previous devices.

4 CHAIRMAN HEFFEZ: Okay. Thank you.

5 I would like to move forward with the
6 primary reviewers. There will be three primary
7 reviewers: Dr. Rekow, Dr. Burton and Dr. Janosky,
8 and we'll go in that order. I'll allot 15 minutes
9 maximum for each one, to be followed with five
10 questions.

11 Dr. Rekow.

12 DR. REKOW: Well, I won't use up my 15
13 minutes.

14 I think that there are a couple of
15 important points to make. I think that the
16 corporate issues have made it a point to address the
17 ASTM and ISO standards, and I think that most of the
18 testing that was done and proposed follows issues
19 that were completed before the IDE submission, and I
20 think that -- is that a proper statement, Susan?

21 CHAIRMAN HEFFEZ: Dr. Runner.

22 DR. RUNNER: The testing was approved

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with the IDE, but before the PMA submission.

DR. REKOW: Right, and so much of this has been reviewed before. And so I think that we need to keep that history in perspective.

Well, we still need to address the issues of the safety and efficacy, but we do need to identify that much of this testing was done some time ago.

In my opinion, as I looked at the different designs as I understood them from the drawings and the information that was presented to us, there has certainly been an evolution in the designs, but from my assessment those typically have not changed minimum thicknesses, nor have they made radical changes in areas that would be the most likely high stress concentration areas.

So I think that the tests that have been done, while there have been changes in the design, don't remarkably change the anticipated results, with perhaps the small exception of the pre- and post peg question, and that is being addressed now.

I have a small concern about whether or

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1 not the test that was originally designed, where you
2 don't have a compliance substructure to adequately
3 give you the failure mechanisms under fatigue
4 loading, but indeed, they are providing information
5 that will be able to be correlated with the
6 historical testing, and so it's an interesting
7 question about which of those is the most
8 appropriate approach to take.

9 A couple of other concerns that I think
10 may need to be addressed as part of our concern is
11 some of the testing was done with bovine bone
12 thicknesses. I believe that was the pull-up test.
13 No. Was that the pull-up test that was done?

14 And there the cortical plate was argued
15 to be twice as thick as the cortical plate in the
16 mandible, but you would put your screws through both
17 sides of the mandible.

18 And if that's true that you really go
19 through the whole cortical plate on both sides of
20 the mandible, it's a good argument. The question is
21 how much of the second side of the cortical plate
22 the mandible gets engaged in the screws. I think

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1 that that's not a critical issue. I think it's one
2 that just needs to be addressed, needs to be thought
3 about a little bit.

4 I am slightly concerned with some of the
5 issues that Dr. Li has brought up about the creep in
6 the fossa component, and more particularly about the
7 wear debris and the scenario of the wear debris
8 because that historically has been such a remarkable
9 issue.

10 I would encourage you to look at the
11 wear debris with your new testing and to do it
12 rather aggressively, and if you find things perhaps
13 you might want to propose some other testing be done
14 to either allay fears or to change your design.

15 I think though that it's also important
16 to note that these are the materials that are being
17 used in other applications, and they have succeeded
18 in other clinical applications. So I don't think
19 that the concerns that I'm raising should be
20 alarmist concerns, but I do think that we need to
21 know a little bit more about the wear debris and its
22 outcomes because that to me is a singular issue that

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1 could potentially create some very difficult in vivo
2 problems.

3 CHAIRMAN HEFFEZ: Any questions to Dr.
4 Rekow from the panel?

5 (No response,)

6 CHAIRMAN HEFFEZ: Then we'll move to Dr.
7 Burton.

8 DR. BURTON: Richard Burton.

9 I'll try to deal just strictly with the
10 clinical issues. Many of these, as of the issues
11 that I found in my review, have already been
12 answered, and I'll just try to sort of maybe perhaps
13 raise them and close some of the questions at the
14 same time.

15 In reviewing obviously from a clinical
16 standpoint, I looked at the complication rate, which
17 I would agree is certainly within the norms for this
18 type of patient population in my experience. The
19 type of complications which we saw, again, is that
20 we saw there were only eight explanted joints. Most
21 of those result, sometimes not spontaneously but
22 within normal conservative management techniques,

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1 and the most common ones being neuromas and various
2 scar tissue adhesion type of issues, which, again,
3 are very common in this type of population.

4 And as Dr. Quinn pointed out, the issue
5 of heterotopic bone with both TMJ surgery and with
6 any type of implant. Over the years we have seen
7 that to be a constant source of problem, one which
8 at least at this juncture has not had a good answer
9 for that.

10 The concern I had in looking at the
11 complication rate is that just sort of anecdotally
12 as I reviewed the entire patient population and the
13 patient key for that, my sort of gut feeling was the
14 fact that there certainly had been somewhat of a
15 decrease in rate as you went further on in the
16 study, which again would play into the fact of
17 experience, time issues, and time of surgery issues,
18 which Dr. Quinn explained as well, and I would
19 certainly make the comment that in having treated
20 patients for a number of years where you had
21 unilateral TMJ problems, that once you improve their
22 primary complaint site, suddenly the site which had

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1 not been their primary complaint, oftentimes they
2 would return regardless of the type of procedure
3 that was done in saying, "Gee, this site is really a
4 lot better. Now my other site."

5 And you know, you raised the question
6 whether or not that was a shift in load. Many of
7 us have asked ourselves that question over the
8 years, and this is certainly within the realm of the
9 possible. Many times, I think, most of us have felt
10 that that was a fact, is that the patient becomes
11 aware of those symptoms. Like most of us, you know,
12 if you have one primary complaint, once that's
13 addressed sometimes you move on to more secondary
14 issues.

15 Review of the surgical indications I
16 thought were adequately explained because I had some
17 concern regarding the ages with that. I would
18 concur with Dr. Quinn in the fact that I think that
19 avascular necrosis is a vastly overplayed term,
20 which has become sort of a popular catch-all for
21 some unexplained situations, and I think that we've
22 sort of allowed some time to our radiographic

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1 colleagues to sort of push us towards that diagnosis
2 where many of us clinically are not quite sure that
3 that exists to that level.

4 I did have some concerns regarding the
5 issue of site bias and the fact that, again, if you
6 looked at the original protocol and you were talking
7 300 patients, which I thought was quite laudable,
8 but again, a reasonably large group, in ten sites
9 would have been good.

10 But again, the point where we have eight
11 surgeries done by three additional sites, I have
12 concerns whether the complication rate that we're
13 currently seeing, which is both reasonable in both
14 the type and the numbers, may be a reflection of the
15 fact of the experience level of those surgeons
16 placing the devices and whether as we expand the
17 number of sites, were this product approved, whether
18 we're going to seek a concomitant increase in the
19 rate of complications.

20 The change from a clinical standpoint,
21 from a cemented to a noncemented fossa I think Dr.
22 Quinn addressed, and again, in looking through their

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1 surgical guide, they had developed -- did you
2 develop the burr, the burr that you're using, that
3 diamond burr, for fossa contouring? It was
4 specifically designed for that.

5 Most of us who had used other systems
6 found that that was very problematic, and I think
7 that that's where the need for cement came from. I
8 think that most of us feel, again, any factor you
9 don't have to introduce into that area reduces that,
10 and I guess that's not something that personally I
11 have that change to be much of an issue. I think
12 that that, candidly, an improvement.

13 My last concerns work primarily around
14 the labeling issues, that we have an adequate review
15 of the labeling and indications for that, and then
16 again, this has been addressed several times as a
17 clinician, the fact that I think this is going to be
18 quite dependent upon having an adequate training
19 program such that it will release into broader use
20 of hands, we'll continue to see what are reasonable
21 clinical outcomes with that.

22 And then lastly, like I said, just the

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1 life span issue, that's very difficult to explain,
2 but every patient's idea with various devices always
3 has to say, "Well, gee, how long is this going to
4 last me?"

5 Certainly we can't give them that
6 answer, but looking historically at other issues we
7 need to be able to provide some type of answer to
8 that.

9 And then from a nonclinical standpoint,
10 I think Dr. Li's question of wear debris because it
11 has been my experience that everything has some wear
12 debris, and again, usually if you're not seeing it,
13 you're just not looking at the right level to find
14 that.

15 I'll take any questions.

16 CHAIRMAN HEFFEZ: Any questions? Dr.
17 Bertrand.

18 DR. BERTRAND: Peter Bertrand.

19 Concerning the longevity of the device
20 being implanted and the statement that you made, Dr.
21 Quinn, concerning that most of these patients
22 probably have 18 to 24 hours of tooth contact a day,

1 either pre-surgically or post surgically is any
2 attention given to the ability to control tooth
7 contact?

4 It's been pretty well established
5 through neural science that one *of* the strongest
6 brain responses to incoming stimuli is either tongue
7 bracing or tooth touching. Has there been any work
8 done towards addressing that?

9 Which if you reduce that 18 to 24 hours
10 *of* tooth contact, it might in the long run improve
11 the longevity of the appliances implanted.

12 DR. BURTON: I would say that, you know,
13 that's something that possibly could and probably
14 should be addressed. Again, you have the
15 possibility with any type *of* device that you've
16 taken the patient who certainly has what may be a
17 degenerative joint disease or something else, which
18 is a clinically identifiable pathology, if you want
19 to call it that, who also has underlying
20 neurophysiological issues.

21 And I think that at least what I get
22 that you're asking is once you made, you know, the

1 surgery deals with the more overt clinical
2 pathology, but then once you have addressed that,
3 should you then turn around and try to address
4 perhaps an underlying neurophysiological issue which
5 in a sort of, you know, which came first, the
6 chicken or the egg, but at that point in time
7 perhaps, yes, they may need -- a person who failed
8 surgical or non-surgical therapy and has a surgery
9 may still be a candidate for some nonsurgical
10 therapy which then may extend the life of their
11 implant.

12 That would be my sort of professional
13 opinion on it.

14 DR. BERTRAND: Dr. Quinn, is there any
15 either pre-surgical or post surgical way of
16 addressing that tendency that you made reference to?

17 DR. QUINN: I actually agree with Dr.
18 Burton. There is continuing nonsurgical therapy.
19 It doesn't end with the implantation. I think the
20 question is -- and I'm not sure I could answer it --
21 is the chicken or egg question. Do people brux
22 because they have pain or do they have pain because

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1 they brux?

2 My anecdotal evidence is that if you
3 reduce the pain levels, we do see a reduction. It
4 wasn't a variable we followed, but it would be an
5 interesting one to look at. My impression is that
6 as the pain levels dropped we see less, but we still
7 have people who continue to brux afterwards.

8 And I think to Dr. Li's point and your
9 point, we will continue to use splints to
10 theoretically unload the joint afterwards, which
11 would theoretically decrease wear, but you know
12 there are patients that no matter what we do, I've
13 seen them brux right down to the pulp of the teeth.
14 They're very difficult problems.

15 DR. BERTRAND: Thank you.

16 CHAIRMAN HEFFEZ: Dr. Runner.

17 DR. RUNNER: So this is Susan Runner.

18 Dr. Bertrand, are you suggesting that
19 there could be a labeling issue regarding
20 postoperative treatment of these patients in terms
21 of addressing this issue specifically?

22 DR. BERTRAND: I'm not sure that the use

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1 of a mouthguard is going to actually decrease the
2 amount of loading over time on an appliance that has
3 been surgically implanted. I think the way any type
4 of cranial nerve mediated motor reaction occurs is
5 neurochemically facilitated by incoming stimuli, but
6 there are emerging ways to address that that is
7 coming out in neuroscience which might enhance the
8 longevity of any type of device placed into an area
9 of the body that's controlled by cranial nerve
10 reactions.

11 CHAIRMAN HEFFEZ: Dr. Schechter.

12 DR. SCHECHTER: Dan Schechter.

13 Dr. Burton, with respect to your concern
14 about the number of sites and potential bias in
15 there, how comfortable or what is your opinion with
16 the sponsor's response regarding the population of
17 available patients and available surgeons with
18 appropriate patients?

19 DR. BURTON: I think that they're
20 attempting, you know, to address that topic. My
21 concern is a surgeon, and I'm one, you know, that
22 exists in a, you know, university training

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1 environment where, again, we tend to see -- you
2 know, there are certain procedures where we do --
3 and we're probably the only people in our state, and
4 being a sparsely populated state that performed
5 those, is that this appears to be something at least
6 from what Dr. Quinn was saying is probably more
7 appropriate in a limited number of sites, hopefully
8 more scattered about the country.

9 And I mean, that's not something we or I
10 should say that I think that the FDA controls, but I
11 think that you have to have some assurances that
12 there is going to be an adequate training level
13 because we have seen, looking back historically not
14 only in oral surgery, but in certainly other areas
15 that things work very well in certain surgeon's
16 hands, and sometimes those are the individuals that
17 develop that they have both the expertise and the
18 experience to do that when, unfortunately, both
19 devices and techniques get into less experienced
20 hands.

21 You suddenly discover that complications
22 that nobody dreamed of suddenly start to come out

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again, and we see other adverse effects and adverse outcomes from that, and again, you know, certainly the sponsor of the company can't guarantee that, but I think that as much as they can address that educational issue and how the devices are released to other surgeons at least can be examined.

And I think they've tried to address that, but that's my biggest concern, is when you have things that work well in certain people's hands and certain levels of experience that doesn't translate well to the general population of providers and practitioners that are out there.

CHAIRMAN HEFFEZ: I'd like to move on to the next reviewer. Dr. Janosky.

DR. JANOSKY: Janine Janosky.

I have four primary issues that I wanted to spend some time talking about and discussing, and they are the issues that I primarily have been spending time talking about this morning also, as well as some other panel members have been talking about.

The number one issue is the issue of

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1 follow-up. If we look at the primary outcome
2 measure, the primary outcome measure is a three-year
3 measurement, and irrespective of how we measure
4 that, we come down to about 45 people, and of those
5 45 people, you have 11 of them that are noncemented.
6 So you even have a subset of the 45 that is quite
7 small, and that's actually that noncemented group is
8 about ten percent of those that had started the
9 study. The 45 is about 25 percent of those that
10 have started the study.

11 So the issue then becomes: for primary
12 outcome measures is 25 percent follow-up acceptable?
13 Depending upon what criterion we will use, for the
14 most part we would conclude that that would not be
15 an acceptable level.

16 So then the issue becomes why is the
17 follow-up so low. Revolving enrollment, that's
18 understandable, but then why are we looking at the
19 PMA today as opposed to when most of that enrollment
20 would be?

21 Some of the issues to try to get at why
22 the enrollment was or why the follow-up is so small

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1 I tried to deal with in terms of hypotheses that the
2 sponsor had presented to us, and one of those issues
3 is: could you get some of the outcome measures, but
4 not all of the outcome measures, given the fact that
5 two of the outcome measures are paper and pencil,
6 and we could ask the patients to respond on the VAS
7 scales and send them back to their provider.

8 And the answer was that we don't have
9 missing data irrespective of the type, and so
10 there's some confusion as to whether there was,
11 there wasn't. But I had taken a look at the data
12 and the spreadsheet that was presented to us, and if
13 someone is missing one of those measurements,
14 they're missing all three of those measurements.

15 So that raises some concern to me as to
16 why weren't they at least given the opportunity to
17 provide the data for those that they can do using
18 mail.

19 So the issue of follow-up, it
20 encompasses all these other issues that I'm talking
21 about, but for an event of 45 for three-year follow-
22 up, which represents 25 percent, is that reasonable

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