

1 at that point? So that the answer that we got back
2 and which we provided the agency was based on the
3 statistical analysis performed by the CRO, there was
4 no need to adjust the sample size.

5 DR. SHARMA: But for the final analysis,
6 when you do interim analysis, there is adjustment for
7 Alpha to accommodate the analysis done earlier. And
8 I don't see that in the final analysis.

9 DR. LYNCH: That was an issue that we
10 discussed with the agency very carefully. I'm not
11 sure if we should address that now or if we should
12 wait and let the agency have their time and present
13 that.

14 DR. RUNNER: Well, I think when we have
15 our statistical presentation, that may be --

16 CHAIRMAN SUZUKI: This is Susan Runner
17 speaking.

18 DR. RUNNER: I'm sorry, Susan Runner.
19 When we have our statistical presentation, that may
20 be addressed.

21 DR. SHARMA: Okay. Thank you.

22 CHAIRMAN SUZUKI: Okay. If there's no

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1 other questions we'll take a 15 minute recess.

2 (Whereupon, the proceedings in the above-
3 entitled matter went off the record at 10:31 a.m. and
4 went back on the record at 10:47 a.m.)

5 CHAIRMAN SUZUKI: I'd like to try to stay
6 on time and begin the next part of our session and to
7 begin with, a presentation by the FDA on GEM 21S and
8 our first presenter is Dr. M. Susan Runner, Chief,
9 Dental Division Devices Branch and Deputy Director.

10 Dr. Runner?

11 DR. RUNNER: Thank you. This morning I'd
12 like to have FDA give you some input or give you some
13 input on our feeling about GEM 21S and this morning
14 we'll start with the presentation by Ms. Angela
15 Blackwell, who is a biomedical engineer in the Dental
16 Devices Branch, who will review some general
17 information about information submitted in the PMA
18 and go over device characterization and some
19 submitted pre-clinical studies. Then I will go over
20 some of the issues with the study protocol, clinical
21 results and submitted device labeling and then Ms.
22 Judy Chen from our office will also go over a brief

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1 statistical analysis.

2 And just one additional comment, FDA has
3 received some additional information from the company
4 which was not included in your panel pack. However,
5 we will not be discussing that information today. It
6 will not be discussed by the company or FDA because
7 it has not had time to be reviewed by the Agency, but
8 that's just for your information.

9 MS. BLACKWELL: GEM 21S is a combination
10 product which consists of a device bonding material
11 beta tricalcium phosphate and a drug, recombinant
12 human platelet growth factor. This product is
13 regulated as a Class 3 PMA product. GEM 21S is
14 intended for the management of interosseus
15 periodontal defects. Beta TCP is classified for
16 dental indications in 21 CFR 872.39.30. For dental
17 indications beta TCP was viewed as a drug by the FDA
18 for the device amendments. After the adoption of the
19 device amendments, it was transferred to CDRH as a
20 transitional device. This made it automatically
21 Class 3 and subject to PMAs.

22 Beta TCP for dental indications still

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1 requires a PMA but a proposed rule to reclassify beta
2 TCP and other bone filling materials to Class 2 was
3 published on June 30th, 2004. Under the Orthopedic
4 and Rehabilitation Devices Panel beta TCP is
5 regulated as a Class 2 device.

6 rhPDGF is regulated as a therapeutic
7 biological product in our Center for Drugs and
8 requires a biological licensing agreement. Prior to
9 submission of the preliminary protocol, it was
10 determined that this combination of product would be
11 regulated under a PMA and that CDRH would be the lead
12 review center. CDER would act as the consultant
13 center.

14 The beta TCP component in this submission
15 is regulated for orthopedic indications as Vitoss.
16 Other beta TCP products are regulated for dental
17 indications under PMA regulations. In addition, when
18 beta TCP is combined with other dental bone filling
19 materials, it's regulated under 510K.

20 Dr. Runner will now review the PDGF pre-
21 clinical data and the clinical data.

22 DR. RUNNER: I'd like to go over some of

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1 the safety data that was submitted to FDA that
2 indicated that GEM 21 should be safe for the stated
3 intended use prior to the initiation of the clinical
4 study. The previously submitted data submitted by
5 the sponsor relating to recombinant PDGF consisted of
6 in vitro data, animal data and data from human
7 feasibility studies as well as data from the diabetic
8 foot ulcer study for the Regranex drug product. The
9 in vitro data, as you've heard, consisted of
10 biocompatibility studies, studies of the effect of
11 PDGF on cultured cells and studies of PDGF released
12 from grafting materials. The animal studies, as you
13 also heard, consisted of the evaluation of the
14 effects of recombinant PDGF on bone healing in
15 several animal models.

16 The clinical studies as was also reviewed
17 by the company consisted of human feasibility studies
18 as well as the pivotal studies related to the
19 Regranex product. In addition to review of all of
20 these information prior to the approval of the
21 clinical study, FDA did a review of our adverse event
22 data bases. This was for both the drug product,

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1 Regranex and as well as for the device component of
2 beta TCP. The review of these data bases
3 revealed that the relevance of the data in the data
4 bases was of little significance or questionable
5 significance relative to this product. As you heard
6 from the sponsor, previous effectiveness data from
7 preclinical and feasibility studies have indicated
8 that this product may effective for the stated
9 intended use. Based on these safety data and
10 effectiveness data, FDA approved the IE study for GEM
11 21S.

12 Just to go back a little bit, you've
13 heard a little bit about Regranex. The product was
14 cleared for diabetic foot ulcer treatment and the
15 data came from three large Phase 3 clinical trials
16 using the product of rhPDGF in a vehicle. The
17 product, as you heard, is known as Regranex. The
18 primary end point for these diabetic foot ulcer
19 studies was the percent wound closure after 20 weeks
20 of daily application of approximately .1 mg/ml
21 rhPDGF. Regranex was found to be safe to use and was
22 approved but the wound healing results were not

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1 statistically significantly better than good foot
2 care alone.

3 As you heard, the sponsor submitted a
4 pivotal clinical study to try to assess the safety
5 and effectiveness of GEM 21S in the management of
6 interosseus periodontal defects. The study
7 hypothesis, as you also heard, was that GEM 21S
8 promotes greater soft tissue and bone regeneration as
9 measured by clinical attachment level and
10 radiographic bone measurements than beta TCP alone.
11 As you also know, there were three treatment groups,
12 a low dose, high dose and a control group.

13 The measurements, as you also heard,
14 included pocket depth probing, clinical attachment
15 level, gingival recession and radiographic
16 measurements of linear bone gain and percent bone
17 fill. The primary end point, as stated in the
18 protocol, was the change in clinical attachment level
19 at six months. The sponsor retrospectively added a
20 change in clinical attachment level at three months.

21 In your discussion this afternoon, was will want
22 your input as to the validity of retrospectively

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1 adding an efficacy end point of this type to the data
2 analysis. The sponsor also had secondary
3 end points including linear bone gain, percent bone
4 fill, probing pocket depth and such that has been
5 previously described. These secondary end points, as
6 you know, are used in many bone graft, in studies
7 reported in the periodontal literature and are
8 important parts of this statistical analysis of the
9 clinical study.

10 The sponsor also had secondary end points
11 comparing current data to historical data and those
12 are also being more frequently used in bone grafting
13 studies reported in the periodontal literature. The
14 numbers that are used for both Emdogain and PepGen
15 P15 are a means derived from previously approved
16 PMAs. Many of you may know, we've heard Emdogain and
17 PepGen P15 thrown around a lot today. Emdogain is
18 not a bone grafting material but a gel derived from
19 porcine tooth buds that is applied to root surfaces
20 while PepGen P15 is a bone grafting material
21 containing a synthetic biological response modifier.
22

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1 The linear bone gain and percent bone
2 fill numbers here are also averages derived from the
3 literature. FDA, again, would like your input as to
4 the clinical relevance of the results reported from
5 these end points. In addition to the three-month
6 retrospective analysis end point, the sponsor also
7 added two composite study outcomes and an area under
8 the curve analysis. Both of these analyses were a
9 combination of a clinical and a radiographic end
10 point and tend to be a composite of clinical and
11 radiographic results. Again, FDA would like your
12 input as to the clinical relevance of the results of
13 the area under the curve analysis and the composite
14 analysis.

15 These next tables show the results of the
16 statistical analyses and I'd like you to please focus
17 your attention on the last column to the right where
18 it lists statistical significance for the analyses
19 performed. The first table here compares that low
20 dose to the control group and the next line will
21 compare the high dose to the control group. Please
22 note that the results for the primary end point were

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1 not statistically significant. Please note also
2 which end points were perspective and which end
3 points were retrospective as well as which are
4 statistically significant and which are not.

5 We have a prospective at the top and
6 retrospective at the bottom as you can see. This
7 slide similarly compares the high dose versus the
8 control. For the high dose the only significant
9 results were for linear bone gain and percent bone
10 fill. Again, please note which end points are
11 prospective, which end points are retrospective as
12 well as which are statistically significant and which
13 are not. This table sort of gives a summary of the
14 statistical significance for the study and please
15 note that three statistically significant prospective
16 results were secondary end points.

17 FDA would like you to discuss the
18 clinical relevance of the results reported for these
19 statistical end points as well as the possible
20 importance of the non-significant end point data.
21 The specifics of the statistics will be discussed by
22 Ms. Chen in a little bit. In terms of the safety end

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1 points, as you heard, the primary safety end point
2 was the number of adverse events and as you also
3 heard, most of the adverse events reported in the GEM
4 21S study were associated with the surgical procedure
5 itself not attributable to GEM 21S and this is
6 consistent with other periodontal studies.

7 In the device labeling, the package
8 insert claims these items and the primary device
9 labeling claim was that the GEM 21S was shown by both
10 clinical and radiographic measures to be effective in
11 treating moderate to severe interosseus periodontal
12 defects within six months of implantation. I think
13 it's important to note that in this PMA the sponsor
14 has expanded its indications for use to include
15 deficient alveoli ridges, cystectomy, apicoectomy and
16 treatment of extraction sockets.

17 To summarize the safety data from this
18 PMA, the protocol as you heard, was followed without
19 any protocol violations. There were no safety
20 concerns related to the GEM 21S or its components and
21 the safety data collected were consistent with
22 previous studies. The efficacy summary as

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1 summarized, showed that the study failed to meet its
2 primary efficacy end point. A high percentage of
3 patients completed the study which the sponsor should
4 be commended for. Results from many secondary
5 points, end points, demonstrated statistically
6 significant results and a retrospective analysis was
7 positive for the low dose group at three months.

8 In conclusion, one of the things that
9 we're going to ask you to discuss later today is how
10 we should look at reliance on secondary end points
11 form approval, possible approval of this PMA,
12 reliance on retrospective statistical analyses in a
13 possible approval of this PMA and also the clinical
14 benefit for the addition of the recombinant PDGF to
15 beta TCP. And finally, we would like your input on
16 the expansion of the indications from you -- for you
17 from the simple periodontal indication to the other
18 indications that I mentioned previously.

19 And now, I'd like Ms. Judy Chen to
20 continue with our statistical review.

21 MS. CHEN: My name is Judy Chen and I'm a
22 statistician from FDA. Right now, I will present to

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1 you from my statistical perspective of the clinical
2 studies. I'll just go through these quickly because
3 we have gone through this two times already. This is
4 a multi-center, randomized, three parallel groups
5 trial of 180 patients and Group 1 included beta TCP
6 and plus a low dosage of the subject material PDGF.

7 And the second group is the beta TCP plus
8 the high dose of PDGF and there's the third which is
9 used as the control and that is only beta TCP and the
10 study is blinded and the study size, the subjects and
11 the monitor were all blended to the treatment of
12 assignment, which, of course, is a very good point.

13 The primary effective end point defined
14 in the protocol is the change in clinical attachment
15 level between baseline and the six months post-
16 surgery and the comparisons between the low dose
17 versus the no dose. And the study in the protocol
18 also specified a group of secondary end points which
19 is improvement in linear bone growth and percent bond
20 fill at six months and improvement in clinical
21 attachment level at six months but this is for the
22 high dose versus the no dose. The reduction at six

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1 months, change in gingivae recession at six months
2 and the bone healing.

3 Okay, the study hypothesis is to promote
4 greater soft tissue and the bone regeneration as
5 measured by clinical attachment levels and a bunch of
6 secondary end points. Then an osteo-conductive
7 scaffold alone and also then the historical controls.

8 Statistically, the hypothesis -- the study
9 hypothesis is stated as such; that the objective of
10 the study, we like -- we want to show that the
11 alternative hypothesis of the -- is the 2H1s that the
12 clinical attachment level improvement is greater than
13 1.5 millimeter and also that the clinical attachment
14 level in the low dose group is significantly better
15 than that in the low dose group. In order to do that,
16 we need to reject the known hypothesis which is the
17 improvement in the CAL less than 1.5 millimeter or
18 the improvement in CAL in the low dose group actually
19 is less than or equal to the clinical attachment
20 level in the no dose group.

21 I know that in order to show the
22 effectiveness we need to reject the known hypothesis.

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1 But in doing so, we always will come into two
2 different kind of error rate. One is that false
3 positive error, that is actually where the device is
4 not effective yet it become proven that it is
5 effective. Conversely, the false negative error is
6 that when the device is effective but we concluded
7 that the device is not effective. So both of these
8 error need to carefully controlled. If we don't
9 control this error, both the error rates, we really
10 cannot trust our conclusion.

11 Okay, that was the statistics will help
12 you but the statistics allow us to based on the
13 clinically significant treatment of fact, the
14 expected standard deviation and at acceptable false
15 positive rate it is conventionally use the five
16 percent. We allow five percent positive error, false
17 positive rate. The statisticians can estimate the
18 simple size which needed to test the intended
19 hypothesis, hypothesis with adequate statistical
20 power so we can be able to control the false negative
21 rate.

22 So we will find that the difference in

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1 statistical significant reject known hypothesis and
2 conclude that the alternative hypothesis of device
3 effectiveness is correct. And also subsequently,
4 when we have the data, the statistician can based on
5 the observed data rejected known hypothesis and
6 conclude that adding the PDGF to beta TCP will
7 improve the six months count when the false positive
8 rate is under control.

9 Okay, in the protocol, the symbol size is
10 estimated such that for expected treatment difference
11 of one millimeter with standard deviation of two
12 millimeter, and actually the sponsor used the one-
13 sided false positive rate of .05, which I don't
14 completely agree but that is leave it there for now,
15 and a false negative rate of .2 or a power of 80
16 percent. According to that, 50 patients per
17 treatment group were needed and adjusting for
18 potential missing data, 60 patients were enrolled in
19 the study.

20 So that the study actually has adequate
21 power to detect a treatment difference of one
22 millimeter or larger. That is the false negative

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1 rate is under control in this study. Now, let us
2 look at the result we have after we have the data
3 that mean care improvement at six months are 3.7
4 millimeter in the low dose group and the 3.5
5 millimeter in the no dose group, so that the
6 treatment difference is only .2 millimeter with
7 standard deviation, 2.2 millimeter which is
8 statistically not significant even at the one-sided P
9 value, one-sided P value is .2, that's 20 percent.

10 And also the 95 confidence interval for
11 the treatment difference is minus .35 to .55
12 millimeter. So based on the data, if we reject the
13 end -- the known hypothesis and the claim there is
14 added benefit, the false positive rate, which is one-
15 sided false positive rate will be 20 percent.

16 So this is really very much larger than
17 two-sided five percent value. So now we cannot
18 conclude that device is effective so what shall we
19 do? Can we construct new end points? Can we add
20 more patients, be more helpful? Let's first look at
21 the situation of adding more patients. Well, here we
22 can all see that the observed treatment of difference

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1 is only .2 millimeter which is much smaller than the
2 precision of instrument which is one millimeter and
3 also the study is designed for one millimeter so fail
4 to reject the known hypothesis due to small treatment
5 difference not due to large standard deviation
6 because if it is due to large standard deviation,
7 statistic procedure under limited circumstance will
8 allow several estimation but here the treatment
9 difference is really way too small.

10 And also the blinding is broken so if we
11 do that bias will be a problem. And here just
12 supposed if we would do that, we would add more
13 patient to detect a .2 millimeter difference with
14 standard deviation 2.2 millimeter, the study for what
15 we had, the same size we had in the present study the
16 study's power is only 17 percent. To increase power
17 to 80 percent, we need actually instead of 50
18 patients per treatment group, it needs 750 patients
19 per treatment group.

20 Of course, ultimately the question is,
21 does the difference of .2 millimeter make any real
22 clinical difference? So we're -- no more patients

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1 will not be helpful, so let's look at additional end
2 points. Now, we have set some secondary end points
3 which is specified in the original protocol and also
4 there are new end points which is added later. Well,
5 however, in both situations, you know, the false
6 positive to conclude that a device is effective
7 cannot be controlled like we can for the primary
8 effectiveness end point.

9 Here let us look at the secondary end
10 point that among these six comparisons, at least six
11 comparisons, I only counted the low dose versus no
12 dose, high significant treatment difference is
13 detected in both linear bone growth and the percent
14 bone fill marginally significant difference is seen
15 in total gain measured as area in the curve and the
16 other variables are not even -- didn't -- it's not --
17 didn't even reach the five percent level. However,
18 since we made multiple comparisons, we have to know
19 that. Statistician has long noted that if the
20 critical -- usual critical values are used, or the
21 usual P live I show in the previous slide, when there
22 are multiple comparisons the false positive rate is

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1 greatly increased over the nominal level. So
2 actually what you have just seen are the false
3 positive rate is too small so that the AUC variable,
4 as you recall, the P value, just reached five
5 percent, can now become considered significant but
6 the other two variable, linear bone growth and
7 percent bone fill will still be significant but the
8 are secondary end points.

9 Okay, there are more new -- there are
10 other new end points which is the care at three
11 months and gingivae recession at three months and
12 also there are two additional composite end points.
13 We have gone through this before, when the linear
14 bone growth and the other is bone fill. Here are the
15 raw P values of these new end points. Let's focus on
16 the low doses, that's the subject therapy that you
17 can see that both gain at three months and gingivae
18 recession are statistically significant just look at
19 the P value. However, here we made four comparisons,
20 notice the previous slide that for -- if we did
21 multiple comparisons the error rate actually are
22 increased so both these can now become considered

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1 significant so that left with the composite end
2 point.

3 However, they are result based on end
4 points constructed after the blinding. This is my
5 understanding of submission but it certainly is the
6 new end point broken and results on the pre-specified
7 unknown are not reliable. False positive rate are
8 inflated and cannot be statistically adjusted. Okay,
9 there are also results on comparison to baseline
10 values and also here I just compared to standard
11 value of 1.5 millimeter that the improvement for all
12 three treatment groups are all statistically highly
13 significant. However, know that this is comparing
14 the low dose treatment -- this is a comparison
15 between the low does treatment to no treatment, not
16 to the additional benefit by the growth factor and
17 also compared to baseline values. There are other
18 problems such as placebo effect, change due to
19 disease and natural history or regression.

20 So my conclusion for this submission is
21 that data in the pivotal study demonstrated that
22 adding PDGF to beta tricalcium phosphate does not

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1 statistically significantly increase clinically
2 attachment level improvement which is the primary end
3 point. Statistically significant benefit are
4 detected in the secondary end point, percent bone
5 growth, percent bond fill and linear bone growth.

6 The statistically significant treatment I
7 found in the two composite end points CAL linear bond
8 growth and CAL person bone fill are not reliable
9 since false positive rate are inflated and cannot be
10 statistically adjusted. Thank you for your
11 attention.

12 CHAIRMAN SUZUKI: Okay, I'd like to now
13 ask the panel if there are any points of
14 clarification for the presentation at this time. Ms.
15 Lawton?

16 MS. LAWTON: Yeah, I have one question
17 and I don't know whether we should save it for later,
18 but I'm hearing two different things. I thought I
19 heard earlier when the question was asked of the
20 company about when they -- when they came up with
21 these additional end points that it was done prior to
22 data base lock and unblinding of the data, but what

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1 I'm hearing from the FDA is that they were
2 constructed after the blinding was broken and I'm
3 trying to understand which one actually happened.

4 CHAIRMAN SUZUKI: Okay, maybe Ms. Chen
5 can provide that clarification. Dr. Runner?

6 DR. RUNNER: This is Susan Runner. It
7 is our understanding that the three-month look of CAL
8 for the low dose group was a retrospective analysis.

9 If I am incorrect, please correct me. That's
10 correct, that's incorrect? Would you please clarify?

11 MR. BEASLEY: Bill Beasley with
12 BioMedic. The three-month CAL was actually part of
13 the original -- it was an original composite end
14 point that was obtained and it was -- that analysis
15 was done before the data base -- or sorry after the
16 data base was locked. All clinical measurements were
17 analyzed after the data base lock.

18 CHAIRMAN SUZUKI: Ms. Lawton?

19 MS. LAWTON: And can I just follow up,
20 the two composite end points, were they done before
21 or after data base lock?

22 MS. BLACKWELL: This is Angela Blackwell.

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1 None of the composite endpoints appeared in the
2 submission until the PMA arrived, in other words in
3 the IDE study. So they could have been -- so it's
4 not very clear. You know, they were not added to
5 the IDE study before the study started and that was
6 the case with the three-month CAL. The original
7 protocol called for them to gather the data of CAL at
8 three months but it wasn't considered a primary end
9 point. The six-month was a primary end point. It
10 was only after the data was gathered that they came
11 back and said, "Well, we want to depend more on this
12 one because there was a difference in the data".

13 DR. SHARMA: Excuse me.

14 CHAIRMAN SUZUKI: Dr. Sharma?

15 DR. SHARMA: Inder Sharma. My question
16 is at what point the company came over to ask for the
17 analyze at three months? Was it before the data lock
18 or after the data lock?

19 MS. BLACKWELL: The data was gathered as
20 part of the original protocol. They changed the way
21 they were analyzing things after the fact. So the
22 data was gathered, it was part of the protocol but

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1 they came in later and asked for -- there were some
2 changes in the course of IDE. If you remember you
3 were asking about the change in the dose? That's
4 something that happened during the course, you know,
5 before the data was unlocked but after the original
6 approval.

7 CHAIRMAN SUZUKI: Thank you. Dr. Amar?

8 DR. AMAR: Salomon Amar. And this is a
9 question to the FDA. At a certain point, I believe
10 that the FDA had asked the sponsor to perform a meta-
11 analysis with published data from Reynolds and
12 Genobaly. I want to know what was the rationale
13 behind asking this meta-analysis and was that -- if I
14 understand correctly, was that meta-analysis asked
15 after the blindness was broken, am I correct?

16 DR. RUNNER: I believe it was after the
17 blinding was broken and it was the result of the fact
18 that the primary end point was shown to be not
19 significant.

20 DR. AMAR: The other question that I had,
21 did the sponsor or the FDA and from a statistical
22 perspective, perform an analysis between Group 1 and

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1 Group 2?

2 MR. CITRON: My name is Mark Citron and I
3 spoke earlier and I'm with BioMedics. There appears
4 to be a certain amount of confusion on the
5 radiographic and the statistical analysis as well as
6 the CAL and if I could take just a second to try to
7 explain the dynamics of the process, I was reviewing
8 some of the documentation and it brought to my mind
9 that submission that we made last summer after the
10 data had been collected and we'd always collected CAL
11 and radiographic information. The data base was
12 still blinded to all of us, to the investigators, to
13 the company, to the patients so we never broke the
14 blind for these analyses and what happened was -- and
15 this kind of helps put it in the proper context, when
16 we made the submission and trying to summarize the
17 situation, I indicated to the agency that the
18 revision to the statistical plan provides a change
19 from the original plan in order to add the
20 radiographic assessment in addition to -- and to
21 include a radiographic assessment was in response to
22 the FDA's original request at the study onset, that

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1 the company assess the validity of the radiographic
2 evaluation as an efficacy end point. The collection
3 of the radiographs was pre-specified in the pivotal
4 clinician study protocol. The radiographic analysis
5 conducted appointed fashion and conforms with
6 applicable good clinical practices standards. We're
7 governed by a separate IRB for the protocol,
8 performed by an independent reviewer in a single
9 investigational center that was not involved in the
10 clinical portion of the pivotal study and finally
11 performed after -- after an initial radiographic
12 qualification study demonstrated that the quality of
13 the radiographs supplied by the clinical sites was
14 sufficient to accurately perform the radiographic
15 assessment.

16 In other words, what happened was the
17 radiographs were collected at the onset of the study.

18 They were necessary to do the safety portion of the
19 assessment as part of the interim analysis and then
20 we were required before we used them for any
21 analytical purpose to insure the integrity of the
22 data, the validity of the data, which we did through

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1 a very comprehensive program, separate protocol,
2 filed with the IRB and the results of that study
3 allowed us to go forward with the use of the
4 radiographs, but we didn't do that until we had gone
5 through the process and let's face it, the
6 radiographs were not useful for doing efficacy in
7 three months because they light up and, you know, the
8 data is not valuable.

9 So we needed to wait for the six-month
10 time to get the valuable radiographs to do the study.

11 We continued to blind the study during the entire
12 course of that assessment and only until after the
13 integrity of the data was assessed were we allowing
14 ourselves to go back and unblind it to run the
15 numbers. Is that -- okay. I'm just trying to
16 clarify.

17 DR. AMAR: I was just asking whether a
18 comparison was done between low and high dosage.

19 MR. CITRON: And I'm -- specific to your
20 question, yes, there was an assessment done between
21 the lower concentration of PDGF and the higher
22 concentration of PDGF. In the data tables that were

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1 provided in the panel packet kind of delineates all
2 the differences. The statistical analysis, I don't
3 believe found any statistical differences between the
4 low concentration and the high concentration. The
5 statistical differences were between the .3 mg per
6 mil at the low concentration and the TCP alone.

7 DR. AMAR: At least in regard to the
8 secondary outcome say for example, the one that
9 played the most on Group 1 which is linear bone
10 measurements and percentage bone fill, there was some
11 kind of difference between Group 1 and Group 2. One
12 would say 56 percent, the other one was 33 percent.

13 MR. CITRON: Oh, you mean for
14 radiographic and --

15 DR. AMAR: Yes.

16 MR. CITRON: Yeah, I don't remember the
17 -- yeah, we'll -- we can address that this afternoon.
18 Thank you.

19 CHAIRMAN SUZUKI: Okay, yes, Dr. O'Brien?

20 DR. O'BRIEN: Bill O'Brien, I have a
21 question for Ms. Chen. Early in your presentation
22 you made an objection to BioMimetics and their study

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1 using the one sided test for significance as opposed
2 to a two-sided test for .05, which is often done
3 since the hypothesis clearly stated a test if
4 something was greater. So I can see why they would
5 use a one-sided test. Did you redo that in terms of
6 a two-sided test for your conclusions or did you stay
7 with the one sided test that they proposed?

8 MS. CHEN: Yes, in my opinion *** 11:29.

9 And actually in most case the *** already past. Here
10 we need to show that the combination is better than
11 the tricalcium phosphate alone. *** because we are
12 concerned about whether the experimental group
13 actually turns out to be worse than the control group
14 but *** but in this study the significance never
15 seemed to make any difference in the combination
16 because even looking at taking the one sided the
17 other way for determining the end point is ***
18 between the low dose and no dose is the PR is .2
19 which ***

20 CHAIRMAN SUZUKI: Dr. Cochran?

21 DR. COCHRAN: I'd like a clarification
22 from Ms. Chen as well. You said, if I understand

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1 this correctly, that the composite secondary
2 variables was not statistically correct based upon
3 the high negative error rate. How about the other
4 secondary variables that were significant, the bone
5 fill and the linear bone growth, are those valid
6 assessments, the secondary end point verbiage?

7 MS. CHEN: Yeah, since both of them are
8 pre-specified in the protocol, they are statistically
9 -- they are highly significant number so even in the
10 presence of multiple composites I would conclude they
11 are significant but as secondary end point. Why I
12 say it cannot be, you know, adjusted is because I do
13 not know how you put the secondary end point, put it
14 as if they were primary end point because we did do
15 that, taking that end point after the primary.

16 CHAIRMAN SUZUKI: Any other questions
17 from the panel? Dr. Runner?

18 DR. RUNNER: I think that the question
19 you asked and Ms. Chen's response is part of what
20 we'd like you to weigh in on in terms of the clinical
21 significance of what the results of this study are.

22 DR. AMAR: Who selected primary and

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1 secondary outcome?

2 DR. RUNNER: Well, initially the company
3 selected the end points. I believe we requested, if
4 my memory is correct, that we would not like more
5 than one primary end point, is that correct?

6 MS. BLACKWELL: Yes, Angela Blackwell.
7 Initially there were not as many secondary end points
8 as you see here. Initially the company was going to
9 take the radiographs but they did not have something
10 specified that they were going to evaluate them.
11 They were included in the data they were gathering
12 and then later on they said, "Well, we have this
13 data, so we want to analyze it now".

14 We had actually suggested since they were
15 gathering it anyway that they perform some type of
16 analysis. So later in response to us, they came back
17 with the two primary end points and then after they
18 had done the study, then they came back with the
19 composite end points that you saw that were the
20 radiographic and the clinical combined.

21 CHAIRMAN SUZUKI: Dr. Lynch?

22 DR. LYNCH: Just to comment very briefly

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1 on that, I think everybody's statements are correct.

2 The original protocol the CAL was assessed as the
3 primary end point following a pre-IDE meeting with
4 the agency, and the reason for that is that's the
5 primary end point that had been used for both pre-PMA
6 approved products, both Endogain and PepGen. Neither
7 of those products met the statistical end point of
8 CAL for their primary either, very similar to us, but
9 it was felt that since that was the primary end point
10 for the two previous PMA approved products, that that
11 would be the appropriate end point for the study.

12 And then as Ms. Blackwell indicated,
13 based upon actually the FDA's recommendation, we did
14 then add secondary end points, the radiographic
15 analysis of bone fill.

16 DR. AMAR: I guess my question now is and
17 I'm asking that to the statistician, can we
18 retrospectively consider linear bone gain as a
19 primary outcome?

20 MS. CHEN: Judy Chen. They are, they are
21 pre-specified secondary end point and they are -- the
22 secondary are pre-specified but they are secondary

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1 specified as secondary end point. The primary --
2 it's not a primary end point, that's what I want that
3 to be clear. But they are pre-specified and they are
4 statistically highly significant.

5 DR. AMAR: The reason I'm raising this
6 issue is that in periodontal disease and periodontal
7 treatment, it depends on how we look at the success
8 of treatment. If it's viewed as closing of the
9 pocket, it's one of the end point. And if it is
10 viewed as bone gain and regeneration, that's taken
11 from another perspective and then the choice is
12 unequivocal here but if it's taken as closing of the
13 pocket, then that becomes another regenerative issue.

14 That's the reason I'm considering whether
15 statistically we can now retrospectively take linear
16 bone gain as a primary outcome and that's -- forgive
17 my ignorance.

18 DR. RUNNER: I think that, you know, just
19 the comment, that's why we --

20 CHAIRMAN SUZUKI: Dr. Runner?

21 DR. RUNNER: Yeah, this is Susan Runner.
22 I think that's what we want you to weigh in on,

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1 given your clinical experience what the clinical
2 significance of the results are.

3 DR. SHARMA: Inder Sharma, may I speak to
4 this? No, you cannot. Yeah, certainly for new study
5 you can plan other end points which are more
6 promising to you as -- or even considering, even I
7 would say based on what you learned from the previous
8 computation that they could not achieve the
9 statistical significance that you're hypothesis could
10 have been non-inferiority or non-superiority
11 hypothesis and there are a lot of other
12 considerations to take into account. But you cannot
13 have the secondary at this point retrospectively
14 extended.

15 DR. LAVIN: Yeah, Philip Lavin. I think
16 that I would agree with Dr. Chen's (sic) perspective
17 that the secondary end points are valid
18 statistically. Where it gets murky and where it gets
19 complicated is the interpretation of the composite
20 end points, but I would stand on and agree with Dr.
21 Chen that the two secondary end points stand alone in
22 terms of their statistical significance.

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1 CHAIRMAN SUZUKI: Dr. Zero?

2 DR. ZERO: Domenick Zero. Since the
3 radiographic analysis is becoming more important in
4 our discussion, I want to go back to the protocol a
5 little bit and my understanding was that the initial
6 radiographs were taken mainly for the purposes of
7 safety to make sure that the subjects that were
8 enrolled met the inclusion criteria. What I'm --
9 we're now taking that information and now moving that
10 baseline forward and then using the six-month
11 radiographs as a way of interpreting the study.

12 The fact that in the protocol, there
13 isn't a very good description of how the radiographs
14 were taken, and the fact that they weren't going to
15 be used as a outcome measure for the study, was the
16 standardization, the training, the condition that the
17 x-rays were captured under, do they meet, you know,
18 what we call scientific criteria for using
19 radiographs as an end point?

20 CHAIRMAN SUZUKI: Dr. Lynch?

21 DR. LYNCH: Sam Lynch with the company.
22 Again, as part of the pre-IDE meeting we had with the

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1 agency, we had this discussion about the radiographic
2 -- the use of the radiographs and you are correct, in
3 the original protocol that was approved, and what we
4 had agreed to do was to collect the radiographs,
5 certainly analyze them for safety purposes as well as
6 eligibility criteria but had agreed as a course that
7 that -- of those discussions that we would look at
8 their validity actually to your very point, as using
9 those radiographs as a basis for measuring bone
10 formation, linear bone growth and percent bone fill.

11 We had a discussion at the pre-IDE
12 meeting as to whether or not -- in fact the agency,
13 again was encouraging us to use those and we actually
14 had gotten some frankly mixed messages as to the
15 validity of using radiographs and what we came back
16 and suggested was that we would collect the
17 radiographs. We then in a separate pre-specified
18 protocol that was fully IRV approved and so forth
19 through Dr. Reddy's site at Alabama, did a
20 qualification study on the first 25 sets of
21 radiographs that were collected, full sets of
22 radiographs, baseline three and six months, to answer

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1 the very question, are these valid, you know,
2 radiographs. And are they useful and could Dr. Reddy
3 do the analysis.

4 It was at the conclusion of that
5 qualification study and based on Dr. Reddy's report
6 which was submitted to the agency, that then we said,
7 "Yes, we do believe that these radiographs are of
8 sufficient quality and that the analysis is
9 sufficiently robust that we could rely on the data
10 that was again, submitted as a formal IDE supplement
11 to the agency clearly specifying exactly what those
12 radiographic end points would be for linear bone
13 growth and percent of bone fill.

14 DR. RUNNER: This is Susan Runner again.

15 I think from our experience with previous
16 periodontal studies, the radiographs tend to be
17 important when it comes down to the final look at the
18 data and I think that's one of the reasons why we
19 suggested that to the company.

20 DR. ZERO: Domenick Zero, just to follow
21 up, there are limitations to what you can do with
22 radiographs after capture based on image analysis or

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1 -- I mean, you can stretch it but you can only go so
2 far and you do approach a quality issue of whether
3 it's acceptable and scientific. So I recognize you
4 can do some post capture modification of a radiograph
5 but there are limitations.

6 DR. LYNCH: Absolutely, Sam Lynch again.

7 And as part of the investigator meeting, prior to
8 initiation of the study is we -- Dick mentioned
9 during the course of our presentation. We did
10 clearly describe with and discuss with the
11 investigators the importance of the radiographs, the
12 standardization technique using the Rand ***
13 instruments and the fact that -- and I think this
14 comes out in the data, that they should analyze those
15 radiographs, you know, clinically, visually, prior to
16 releasing the patients to make sure that in their
17 clinical judgment, the radiographs were of sufficient
18 quality to be you know, analyzed. And so we clearly,
19 you know, made a big point of this with our
20 investigators and I think that the fact that 174
21 cases out of the 178 total cases in the study were
22 able to be analyzed radiographically, speaks to the

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1 fact that again, we and more importantly our
2 investigators were very careful in the quality of
3 those radiographs and if there was a radiograph that
4 had a poor emulation or so forth, they retook it
5 before the patient left that visit.

6 CHAIRMAN SUZUKI: Dr. Cochran?

7 DR. COCHRAN: Yeah, David Cochran. I
8 have another statistical question for all our support
9 statisticians. This product is used to stimulate
10 healing responses and I understand Dr. Lynch's use of
11 six month as their clinical attachment level end
12 point due to the prior submissions that had occurred,
13 which makes a lot of sense, but this product actually
14 as opposed to those previous products, does speed up
15 the healing.

16 So looking at a three-month clinical
17 attachment level certainly makes sense from the
18 mechanism of action. But my question is, by going
19 back and re-analyzing it, does that change anything
20 that we should interpret from a statistical point of
21 view looking at the significance of CAL at three
22 months.

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1 CHAIRMAN SUZUKI: Ms. Chen?

2 MS. CHEN: Judy Chen. Yeah, sure, of
3 course, there has to be modifications. I think in my
4 slide, I don't know which one, that at the three
5 months, the three months CALs comparing to low dose
6 and the no dose, it -- the -- let me try to find it.

7 It's like -- it's quite marginal, that's my point,
8 yeah, three months is .04, but here we just look at,
9 we make four new end points, we didn't even consider
10 the other ones, even just consider four, with
11 multiple comparisons, the P of .04 will not be
12 statistically significant if we consider multiple
13 comparison, which we should.

14 Now we have -- we may and if I can have a
15 clarification actually that for the previous question
16 by Dr. Amar, that about whether secondary or primary
17 end point, how do we consider the P value, I have to
18 clarify that I didn't say a secondary end point can
19 be taken as primary end point. What I actually said
20 that statistically that there's no method that we can
21 adjust a secondary end point to a level of primary
22 end point that I know. So I honestly that

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1 statistically we cannot, I don't know and I think
2 that the question has to be clinically determined.

3 CHAIRMAN SUZUKI: Thank you.

4 DR. COCHRAN: Let me follow up on my
5 question, please, that I asked. David Cochran. The
6 data was blinded and had -- was collected, the three-
7 month data, prior to analysis but going back and
8 looking at the three-month time point, although you
9 said that when you make the one comparison, it's
10 marginally significant, but if you did a multiple end
11 point analysis, it wouldn't be significant. But it
12 is significant at three months in the two comparison;
13 is that right?

14 MS. CHEN: Because we have many end
15 points that -- I have a slide that shows --
16 backwards. Yeah, multiple comparison and the
17 significance level. Because we make more than one
18 comparisons, the false positive rate is inflated so
19 that at nominal -- what we see all these P values are
20 nominal value and they are too optimistic that the
21 actual false positive rate is much higher. The most,
22 you know, single adjustment is that if you make four

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1 comparisons, in order to achieve an overall five
2 percent rate of false positive, you need to divide
3 that .05 by four which means, .125, then the P value
4 we have really is much, much -- didn't reach that.
5 It's too high.

6 DR. LAVIN: Philip Lavin, sponsor's
7 statistician weighing in. In response to Dr.
8 Cochran's you know, point about looking at the three-
9 month end point and the six-month end point
10 separately, that was part of my rationale for coming
11 up with the area under the curve and we did send that
12 into the FDA and this was done, you know, before we
13 broke the blind, so the area under the curve analysis
14 was to integrate together the chain from three months
15 with the change from six months, so that we could
16 actually avoid this multiple comparisons question
17 with the AUC.

18 CHAIRMAN SUZUKI: Okay, any other panel
19 questions? If not, we will adjourn for lunch and we
20 will convene at 1:00 o'clock.

21 (Whereupon at 11:48 a.m. a luncheon
22 recess was taken until 1:02 p.m.)

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1 CHAIRMAN SUZUKI: On the record. I would
2 now like to call this meeting back to order. We will
3 now continue on the agenda with the panel discussion.

4 Drs. Amar and Sharma have presentations and will
5 lead the discussion. Dr. Amar will present first.

6 DR. AMAR: Good afternoon. My name is
7 Salomon Amar from Boston. What I'm going to be trying
8 to do with your permission is to summarize. Although
9 you have seen the data being presented this morning
10 by the sponsor, by the FDA, I will summarize the
11 important data and take them into a somewhat a
12 clinical perspective as to what is expected from a
13 product like that if it ever comes into the market.

14 One of the mandates of these Federal
15 agencies is to look for safety and I think that I can
16 address that very specifically that in terms of
17 safety my personal appreciation or evaluation of
18 this component has been such that the product whether
19 taken alone or in combination does not jeopardize or
20 provide important concerns as far as me as a reviewer
21 for the public in being safe to be presented to the
22 public. So the question that comes to the panel is

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1 the efficacy or effectiveness in regards to
2 predicates that are available in the market.

3 One of the questions that comes to the
4 panel is basically considering the statistical result
5 that is there a clinically significant benefit from
6 the addition of the recombinant PDGF $\beta\beta$ -tricalcium
7 phosphate. I got asked this question this morning to
8 Dr. Genco as well as the rest of the Panel and the
9 way I would rest or at least momentarily I would say
10 is that there is some kind of a clinical significance
11 associated with adding the PDGF whether in terms of
12 early wound healing that has been seen or definitely
13 if one is interested into taking linear bone measures
14 and bone fill as an outcome in terms of bone
15 regeneration.

16 We all know the periodontists that are in
17 the room that for maintenance of a tooth in terms of
18 longevity the presence of an increased bone is a
19 factor. I think that this trial, and I would like to
20 congratulate the sponsor because this is, within
21 itself, was well conducted and we cannot allow
22 yourself into comparing, as Dr. Genco said this

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1 morning, two other trials, but within itself, the
2 trial was well conducted.

3 If the outcome from a periodontal
4 perspective or periodontal surgeon is regeneration
5 per se, then the choice is unequivocal. There is
6 clinical significance as compared to either other
7 product or as compared to itself, the control. If,
8 now, closing of the pocket is an outcome, we can
9 consider that there is a significance after three
10 months. Although that significance doesn't hold on
11 because β -tricalcium phosphate closes also at six
12 months, but there is no bone support underneath.

13 So it all depends. It does catch up to
14 the control, but the control doesn't have bone
15 filling as was to the β -tricalcium phosphate with
16 PDGF of having bone fill and that's a little bit of
17 the perspective that I wanted to bring to this panel.

18 Furthermore, I didn't have a chance this
19 morning to address the sponsor, but I wanted to know,
20 and that you could address later on, why gingival
21 index, bleeding index and plaque scores there are
22 across the board that take any multiple clinical

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1 trials as being standardized, the index not being
2 used in these studies as opposed to a Lowborn (PH)
3 1986 scale that in all likelihood was just by a few
4 trials. So the comparison with other measurement, in
5 addition to the fact that the way I looked at this
6 scale, is a little bit more subjective as opposed to
7 a bleeding and probing being there or not there or
8 bleeding the Eastman index of putting the stroking
9 into the pocket, determining to us presence of
10 inflammation and not presence of inflammation. That
11 would have been a better marker of wound healing in
12 that area. In addition to the fact that pre- and
13 post-computer digitized image were not taken and that
14 could have an issue and it still is a remaining
15 issue, although this was somewhat addressed but not
16 to complete satisfaction.

17 In terms of the result, I summarize the
18 result. There is clinical significance in terms of
19 clinical attachment levels at three months, but there
20 is no differences with the control and that could
21 well be the case as opposed to if an individual is
22 interested into maintaining and looking at

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1 regenerative procedures, bone is a component and a
2 major factor of over that and clinical significance
3 was achieved over there.

4 The other concern that I had, and I tried
5 to vocalize that this morning, is that I haven't
6 seen a comparison between Group I and Group II which
7 is low dose v. high dose. I'm going to tell you why.

8 The way I look at it at this point is that to my
9 understanding Group II did not perform or performed
10 worse in terms of bone healing as well as linear
11 measurements, 56 percent as compared to 33 percent.
12 The linear measurements were 2.4 millimeter for the
13 low dose as opposed to 1.5. That's a little bit of
14 a, I would say, "detrimental effect" in terms of the
15 bone.

16 My question to the sponsor is that
17 shouldn't we be concerned by a practitioner using
18 several dosage for several grafting area and
19 therefore increasing the local concentration of PDGF
20 reaching probably 0.75 milligram or 1 milligram and
21 reaching detrimental conclusion or detrimental bone
22 support on that. So given that Group II had poorer

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1 results than Group I, I would be concerned about
2 grafting multiple sites at this point and that would
3 be one of the recommendations.

4 As I said earlier, adverse events are not
5 an issue. Here it was concluded recently from the
6 FDA that the mode and the ERS data that are an
7 adverse event, the database reviewed, do not have too
8 much relevance to this product probably because any
9 adverse event that was reported separately from each
10 of the components was due to patient underlying
11 conditions. So a risk benefit analysis was performed
12 according to the IS. So I indicated that the benefit
13 of using the device outweighed the risk associated
14 with itself. Body compatibility appears to be safe
15 and intended to use. Now like I said, I will
16 reiterate some of the concerns that I had, concerns
17 all raised at this point for lack of information to
18 the practitioner regarding safety in large and
19 multiple defects where PDGF local concentrations
20 could raise to a substantial level that could lead to
21 a bolus concentration and therefore, bring to poor
22 result.

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1 The clinical study data component of the
2 device really did not include two areas for which the
3 device did not perform well as opposed to 3-wall
4 defect and 1-wall defect. So my recommendation, if I
5 may say so? Although there are several criticisms in
6 regard to the IDE study, one of them was mentioned
7 this morning where the sample size was too small as
8 well as the analysis of 1-sided t test could have
9 been, 2-sided t test could have been, better for the
10 analysis.

11 But even taking into consideration the
12 criticism, I tried to bring to this panel the
13 perspective that there is clinical significance as
14 compared to predicate in the market. Therefore, I
15 would recommend approval of the component with
16 several considerations. Thank you very much.

17 CHAIRMAN SUZUKI: Thank you, Dr. Amar.
18 The next presenter will be Dr. Sharma.

19 DR. SHARMA: This is Inder Sharma.
20 Looking at the data I reviewed presented by the
21 company as well as data was provided to me by the
22 FDA, it appears to me the device is safe. As to

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1 effectiveness, the data is a little bit mind-boggling
2 to understand why it's working for low dose and not
3 working for high dose.

4 There could be several reasons there,
5 maybe looking at a more understanding of the
6 population and are there any factors which are
7 confounding the issue. So there would be an
8 important thing to be considering for maybe a future
9 study to be conducted to redesign the study with
10 appropriate end points and appropriate stratification
11 is it is necessary.

12 Based on efficacy data, I would suggest
13 that these are some of the things which should be
14 clearly looked into that whether we want to go with
15 also superiority or non-inferiority. But it's
16 possible there may not as much room. It's always
17 harder when both are active devices or drugs. It's
18 harder to prove unless you have a very large sample
19 size and it depends on also a choice of endpoint. If
20 there is an endpoint which can show a significant
21 difference, sizable, clinically-meaningful
22 difference, then you can even have a smaller sample

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1 size and still be able to prove your point whether
2 you take superiority or non-inferiority. So these
3 are some of the considerations to talk through,
4 looking at and revisiting the design of the study to
5 get a superiority kind of claim.

6 In terms of just by itself, I see
7 effectiveness is there in all the three groups. All
8 the three groups are proving that to a certain
9 threshold they are all working. So I see the
10 effectiveness there, but in terms of superiority, I
11 see that that's where the challenge is. To
12 understand the design, to understand the population
13 and maybe reading through that future study should be
14 conducted to get that kind of claim that you want,
15 superiority. Thank you.

16 CHAIRMAN SUZUKI: Thank you, Dr. Sharma.

17 To guide our discussion, the FDA has a few questions
18 for our consideration. Ms. Blackwell.

19 MS. BLACKWELL: Yes, I'm going to read
20 the questions. They are going to appear on the
21 screen and I think, Mark, you wanted to say
22 something.

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1 MR. CITRON: We'll wait until after.

2 MS. BLACKWELL: Okay, and then I think
3 the Company had some things that they wanted to say
4 after we've gone through the questions.

5 (1) "Clinical Benefit of the PDGF.
6 Preclinical and feasibility study data appears to
7 indicate that the PDGF is safe for use in humans.
8 The primary efficacy endpoint results do not
9 demonstrate a clinical benefit for the addition of
10 the PDGF to B-TCP at six months. Please discuss the
11 clinical ramifications of the clinical attachment
12 level results at three months versus six months."

13 (2) "Endpoints and retrospective
14 analyses. Please discuss the validity and clinical
15 significance of relying exclusively --

16 CHAIRMAN SUZUKI: Excuse me, Ms.
17 Blackwell.

18 MS. BLACKWELL: Yes.

19 CHAIRMAN SUZUKI: Could we go back to the
20 first question?

21 MS. BLACKWELL: Well, I'm reading through
22 them right now. You'll be able to see them again.

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1 CHAIRMAN SUZUKI: We were going to go
2 through each one at a time.

3 MS. BLACKWELL: Okay. Well, hold on.

4 CHAIRMAN SUZUKI: Panel members, is there
5 any discussion on question number one? Dr. Cochran.

6 DR. COCHRAN: This is David Cochran. I
7 think it's important for us to keep in mind several
8 things that are going on here. One is that we're
9 looking at lesions that are very complicated
10 biologically that a lot of different factors are
11 coming and going during the healing process and it's
12 not a simply system we're looking at where we're
13 looking at one type of tissue that has to regenerate.

14 We're looking at multiple types of
15 tissues. So when you're looking at product that's
16 going to stimulate regeneration and you're delivering
17 it at one point in time, I think that we have to
18 consider that there are going to be multiple issues
19 that are going on which are going to cloud the
20 potential significance of the data when you pick a
21 point in time.

22 Secondly, the sponsor has picked an

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1 endpoint that was based on prior PMAs that had come
2 before the panel so they were led to think that six
3 months was a good time point. The other thing I
4 think that's very important is that when you have a
5 product that is going to stimulate healing, the
6 chance of seeing early healing is certainly where you
7 might see the difference based on this type of
8 product. So I think given those types of issues they
9 are very important for us to consider when we look to
10 consider whether this product should be approved or
11 not. Thank you.

12 CHAIRMAN SUZUKI: Thank you. Any other
13 issues or questions from the panel members? Dr.
14 Zero.

15 DR. ZERO: Domenick Zero. Since not
16 being an expert in this area, I would like from the
17 panel or from the sponsors of the application to have
18 a better understanding of the connection between the
19 relatively short-term outcomes and long-term health
20 of the patient in terms of tooth retention, mobility,
21 functionality of the tooth, susceptibility to
22 subsequent disease later on, those issues because

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1 again to make a distinction between these three-month
2 to six-month outcomes without that understanding I
3 have difficulty in making a good decision.

4 CHAIRMAN SUZUKI: Would anyone like to
5 comment on that? Dr. Lynch.

6 DR. LYNCH: Sam Lynch, and again I just
7 want to serve as a moderator here and I think our
8 clinicians should speak to that. So Dr. Genco and
9 perhaps Dr. Nevins could talk to the clinician
10 benefit that was observed in this trial, if that's
11 really the point to the question.

12 DR. ZERO: No, the point is that we have
13 a very short-term clinical benefit. That three and
14 six months is a very short-term clinical benefit.
15 How predictive and how valid is this outcome measure
16 for predicting future health of the patient. In
17 other words, if you have this gain but it's lost in a
18 year, that's a very little benefit to the patient
19 considering the pain, the cost and the various
20 factors the patient has to endure.

21 CHAIRMAN SUZUKI: Dr. Runner.

22 DR. RUNNER: Could I make one comment

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1 just in terms of how we looked at clearing the IDE?
2 In some of our past periodontal studies, we have
3 looked at even a year data and through working with
4 clinicians and representatives of the periodontal
5 clinic community, we've been led to believe that in
6 periodontal research after a six-month period, in
7 particular, you start to get maybe recurrent disease
8 process taking over again and clouding the results.
9 Therefore, that's one of the reasons why we pull back
10 to the six-month timeframe as one endpoint area that
11 sometimes, you can correct me if I'm incorrect, after
12 six months you sometimes get a clouding of the
13 picture in terms of the disease process as a whole.

14 DR. GENCO: I think Susan had stated
15 that.

16 CHAIRMAN SUZUKI: Dr. Genco.

17 DR. GENCO: Excuse me. Bob Genco. Many
18 conferences have been held with the FDA workshops on
19 clinical trial design and this is a very important
20 issue that was originally or let's say maybe five
21 years, nine months. Six-month result holding up for
22 another three, that was the standard. I think what

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1 we all saw was that you could get second episodes of
2 disease. I think that's your question.

3 What about recurrence? The studies from
4 the point of view of looking at risk for periodontal
5 disease, we've done a lot of that work. Previous
6 periodontal disease puts you greater risk for future
7 disease. I mention this morning that one there's a
8 cutoff point about five or six millimeters of pocket
9 depth.

10 If you have less than that, then you're
11 at much less risk of having future disease. So in
12 answer to the question, Solomon's question this
13 morning, so we went from seven millimeter pockets
14 essentially to three or four. So that's good,
15 predictive of long- term health.

16 The second thing, and Ernie Houseman did
17 a lot of this work with us, is looked at the level of
18 bone loss as a predictor of future bone loss. So if
19 we can get more bone to grow, then it bodes well for
20 the future. So I think in terms of those two
21 measures what this product does is it gives us both.
22 It gives us closure of the pocket and that may be

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1 due to the surgical procedure and the care of a
2 plaque control and good suturing, good technique, as
3 much as the product.

4 We understand that, but certainly the
5 bone formation, I think, bodes well for the future.
6 If we can get more bone around the teeth, this
7 predicts health in the future, the best we can.

8 DR. ZERO: Okay, but using the basis that
9 if you have the bone you're better off, you don't
10 have the answer to the question that if you form the
11 bone are you better off.

12 DR. GENCO: Yes, I think the assumption
13 is that if you'd lost it and then you'd regained it,
14 you're better off than if you'd lost it and didn't
15 regain it.

16 DR. ZERO: But it's an assumption at this
17 stage.

18 DR. GENCO: Yes.

19 DR. ZERO: That's what I want to
20 understand.

21 DR. GENCO: I think it's pretty well
22 shown from cross-sectional, longitude and

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1 epidemiological studies. Thirdly, Sig Sacrascki (PH)
2 has just shown that six millimeter pockets harbor
3 pathogenic flora and the shallower ones don't. So
4 there's this cut-off point of five or six that seems
5 to be real in terms of predicting future loss.

6 DR. ZERO: But that speaks to just the
7 CAL outcome.

8 DR. GENCO: Right, but again this is a
9 complex disease and you have to look at all of these
10 issues, the flora, the pocket depth which is
11 reflective of CAL and the bone.

12 DR. ZERO: Okay. Thank you.

13 CHAIRMAN SUZUKI: Dr. Nevins representing
14 the sponsor.

15 DR. NEVINS: Myron Nevins. I would like
16 to address your question, too, with a background of
17 39 years of experience in clinical periodontics added
18 on to my advocacy of education. There is a
19 distinct difference in what we might anticipate with
20 how we approach a patient clinically. But I think
21 it's incumbent upon us or obligatory upon us as
22 clinicians to determine what is in the best interest

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1 of the patient. And I think that's the primary
2 interest to you as a panel.

3 There's a difference between CAL and
4 periodontal regeneration. Given the same grouping of
5 teeth for the same amount of bone loss, if we make
6 the mouth clean and we open the tissue and we clean
7 the roots and more and we put the tissue back without
8 any significant change in the supporting structure of
9 the tooth, we'll see an improvement in the CAL just
10 by eliminating the inflammation.

11 It would be nice to reflect on that as a
12 success and to move on with our career. However, the
13 lack of compliance on the part of our patient
14 population is too evident. There is no report in our
15 formal recordings, our literature so to speak, of
16 patient compliance after five years of being more
17 than 33 percent.

18 Therefore, it becomes incumbent upon us
19 to try to reach the best possible level we can for a
20 patient. Therefore pocket elimination, CAL are all
21 interesting, but the endpoint goal from productivity
22 of every periodontist should be to try to restore the

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1 periodontum that's been lost. Obviously, using the
2 example of a 10 millimeter root, whoever did that
3 this morning, I don't remember who used that number,
4 if we had a 10 millimeter root and we had seven
5 millimeters of bone, we'd be much better than if we
6 had four millimeters of bone.

7 In this instance where we're talking
8 about how we're going to measure regeneration, the
9 radiograph really has to take precedence because
10 although it's not a substitute for histology as I
11 presented this morning, you can not make the mistake
12 of looking at a radiograph and determining that
13 you've achieved regeneration. That's already been
14 demonstrated to be a fallacy with histology, but it's
15 a much better indicator than CAL as to whether you're
16 going in the right direction.

17 Now we've presented a series of matters
18 of information. Granted, it's very difficult to use
19 an active control and fulfill the dream of a
20 comparison between a new product with and without
21 that control. The bottomline is that all of the
22 information that we've provided has been going in the

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1 right direction. I don't think there's any question
2 on anybody's part that our bone measurements as
3 secondary evidence shows that the patient has
4 benefitted.

5 We can't solve the CAL at six months
6 because as David Cochran said, there's so many things
7 going on. We have new cementum being formed, new
8 bones being formed, remodeling of the bone, the
9 periodontal ligament, the attachment apparatus that
10 we may not really have the ability to make a judgment
11 on periodontal regeneration. This may be why all the
12 products stumble when they try to get to this because
13 some products, we mentioned Emdogain, might be 14 or
14 16 months until we really see what the endpoint goal
15 of that is.

16 Your question. The most germane question
17 that may have been asked today other than, of course,
18 the primary what's the patient -- The primary
19 question should be what does the patient benefit, not
20 what is a CAL. The question that you're asking is
21 what happens when you regenerate and you get to six
22 months or you get to six years what's the benefit.

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1 Well, from clinical observation when
2 things go well, we seem to go smoothly indefinitely.

3 This isn't one person's observation, but it's very
4 difficult to do in RCT long term on a group of
5 patients because their compliance is terrible. You
6 can't tell who's going to die, who's going to move
7 away, who's going to become unhappy with the services
8 of your practice or your university or however it
9 goes.

10 We ran into the same thing with the NIH
11 with trying to plan long-term RCT answers with dental
12 implants. There was implant failures and trying to
13 find matched defects to do bone growth for dental
14 implants. There are some things that are hard to do.

15 There are some questions that are difficult to
16 answer with the investigative methodology that we
17 have even in a case like this where I think we've
18 done a pretty good job with an RCT. And 99 percent
19 patient retention, it's almost unheard of.

20 But you still cannot bridge the gap of
21 the unknown. When you hang everything on what the
22 CAL's going to be in six months, you tend to overlook

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1 what is the benefit to the patient. If you can show
2 regeneration of Class II furcation with human
3 histology as we were able to do today, that's an
4 eyeopener. That's something we have not been able to
5 do in 100 years of being periodontists.

6 I mean the American Academy of
7 Periodontology is about 85 years old now, 90 years
8 old, and we're just finally getting to the point
9 where we have a product. We can do this. To get
10 hung up on statistics and overlook the benefits, even
11 they are secondary because you only allowed one
12 primary, may overlook the question you're asking.
13 What is the benefit to the patient and the benefit to
14 the patient is significant. That's our job as
15 clinicians, our job as educators, your job as a
16 panel.

17 CHAIRMAN SUZUKI: Dr. Nevins, this is
18 John Suzuki. As a follow-up question, I guess, Dr.
19 Nevins, would you consider your cohort population of
20 180 patients at six months to be the same at risk for
21 future periodontal disease as other periodontal
22 patients?

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1 DR. NEVINS: I think that these people
2 probably now have been committed to a careful period
3 of observation and unfairly, they've probably been
4 tutored to a point where they may have a better
5 chance of taking care of their mouth because maybe
6 they'll pay more attention. When people participate
7 in a study like this, sometimes they pay more
8 attention than those individuals that go through the
9 daily rigors of the practice because you're taking
10 special records and you're taking photographs and
11 you're doing things that they catch on to the thought
12 that well, maybe they're going to do better. But I'm
13 terribly optimistic with the results that we've seen
14 compared to what I've observed with so many other
15 studies that I've participated in.

16 CHAIRMAN SUZUKI: Dr. Zero.

17 DR. ZERO: Domenick Zero. That just
18 triggers the another question I had. Is this a
19 special population? In other words, was this
20 population preselected because they demonstrated they
21 were able to maintain a 15 percent plaque index?

22 DR. NEVINS: The protocol demonstrates

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1 that these people did not go through a long
2 preparatory period, an observation period, before
3 they participated in the study. These people, other
4 than some exclusionary data that we looked at this
5 morning, basically showed that they had a four
6 millimeter, curving depth intraboning.

7 DR. ZERO: Right, but they weren't
8 selected because of the potential for being good
9 compliers.

10 DR. NEVINS: You know what? I wouldn't
11 be able to do that if I tried.

12 DR. ZERO: Okay.

13 CHAIRMAN SUZUKI: Dr. Zuniga.

14 DR. ZUNIGA: Jon Zuniga. The question
15 has been broached earlier and I guess this is another
16 time to broach it once again. That is can someone in
17 sponsor or on the panel explain the lack of a dose
18 effect on either the CAL, the two, three and six
19 month and translate that to clinical significance?

20 CHAIRMAN SUZUKI: Dr. Lynch.

21 DR. LYNCH: Sam Lynch. We actually -- I
22 don't know how possible it is to put our slides up

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1 because we had a slide prepared specifically to
2 address that question. Is that possible or not?

3 DR. COCHRAN: Jon, this is David Cochran.

4 Let me make a comment on that. It's not unusual for
5 an optimal dose to be lower and give you a better
6 effect. This happens with growth factors a lot.
7 TGF-B, for example, very sensitive to dose response
8 meaning if you go too much, you're going to get less
9 response.

10 Even in the Emdogain data, we've done a
11 lot of work on the enamel matrix proteins. You can
12 get too much of that material as well and the results
13 start getting more and more negative. So I don't
14 think it's a real surprise in any sort of way that
15 there would be an optimal dose that's lower than
16 expected.

17 The fact that you're using a carrier
18 that's going to keep the material around may also
19 contribute to that. There are so many factors
20 involved that are going to influence the amount of
21 the protein that actually gets released there that
22 because you don't continue to get a higher effect

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1 with higher doses is really not surprising at all.

2 CHAIRMAN SUZUKI: Dr. Amar has a comment
3 also.

4 DR. AMAR: Yeah, Dr. Amar. In fact, it's
5 a curve, it's a bell, that you have before and after
6 and you have an optimum concentration in many of the
7 growth factors. I have a question for Dr. Nevins.
8 Dr. Nevins, when you did this 11 patients and you did
9 some histology, were you able to calculate the amount
10 of cementum regenerated above the notch?

11 DR. NEVINS: The histologic analysis was
12 done by Robert Shenk in Bern, Switzerland and he did
13 a histomorphologic analysis. I don't have it at my
14 fingertips, but we did have the radiographs and they
15 were very similar. When the radiographs were
16 measured and we had the histologic measurements, it
17 appeared that they were a very accurate measurement
18 of bone development.

19 DR. AMAR: How about cementum?

20 DR. NEVINS: And cementum. They were
21 both the same level.

22 DR. AMAR: Do you have any idea how --

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1 DR. NEVINS: The cementum was actually
2 coronal to the bone.

3 DR. AMAR: Do you have any idea how much
4 on average -- I guess I'm trying to compare the data
5 and this is an eyeopener as you just said. There's
6 no question about that in terms of doing some kind of
7 trials and having the possibility of doing
8 histological approach is very remarkable. I must say
9 that. All I want to determine is the amount of
10 cementum and try to compare it with what we know on
11 human clinical trials.

12 DR. NEVINS: I realize. I just want to
13 turn my head to Sam and see if he had -- Do you
14 remember the analysis of the cementum from Shenk?

15 DR. LYNCH: Just as you alluded to, it
16 was to the place slightly coronal.

17 CHAIRMAN SUZUKI: Can you come to the
18 podium please, Dr. Lynch?

19 DR. LYNCH: It is always coronal to where
20 the bone level is and there's a periodontal ligament
21 and you can always see the epithelial edge and stuff
22 and, in short, the cementum. I didn't come here

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1 prepared with the numbers in that study
2 unfortunately.

3 DR. AMAR: Are we talking about two,
4 three, millimeters?

5 DR. LYNCH: I think you're talking about
6 four millimeters.

7 DR. AMAR: Four millimeters.

8 DR. NEVINS: If you look at that canine
9 data, it was 70 percent bone fill but as we pointed
10 out this morning, it was about 36 percent
11 regeneration in the canine, but the bone fill was
12 pretty dramatic.

13 DR. AMAR: Above the cementum.

14 DR. NEVINS: Yes, but the cementum always
15 runs above the PDL and the bone. Ron's exactly
16 right.

17 DR. AMAR: No, I'm trying to bring this
18 into the perspective, the Bower's study, if I
19 remember correctly.

20 DR. NEVINS: Bower studied the average
21 cementum if I'm not wrong and it was 1.8.

22 DR. AMAR: 1.2.

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1 DR. NEVINS: Okay.

2 DR. AMAR: I'm just trying to --

3 DR. NEVINS: It was 1. something. In
4 this instance, I think it was more 4. something.

5 CHAIRMAN SUZUKI: Okay. Dr. Lynch was
6 going to comment on the inverse relationship of the
7 dose or was that answered?

8 DR. LYNCH: Unless there were further
9 questions, I think that was answered.

10 CHAIRMAN SUZUKI: Are there further
11 questions on the dose?

12 DR. NEVINS: Dr. Amar, did I answer your
13 question?

14 DR. AMAR: Absolutely.

15 CHAIRMAN SUZUKI: Dr. Zuniga.

16 DR. ZUNIGA: Dr. Zuniga. In relation to
17 a practical as a surgeon who's approaching the site
18 and may be size dependent on the site, you have a
19 prepackaged unit. You might be tempted to put two of
20 those units in or three of those units in or two
21 number 18 is too close to 719, in the relationship.
22 There are questions that you might be two no. 18, 17

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1 or 16, whatever, and you have a large accumulation in
2 an area. Is that a negative? Are you now going over
3 a certain threshold of effectiveness? That has not
4 been defined to that.

5 DR. COCHRAN: This is David Cochran.
6 That was Dr. Amar's concern.

7 DR. ZUNIGA: Right.

8 CHAIRMAN SUZUKI: Dr. Lynch.

9 DR. LYNCH: I think we have several
10 people that would like to respond. Dr. Giannoble,
11 would you care to respond?

12 DR. GIANNOBLE: So the issue regarding
13 the dose applied, it was the dosing that was utilized
14 in this study included a concentration. So the
15 grafting material received the application of the
16 growth factor, the PDGF, at either the 0.3 milligrams
17 per mil dosage or 1 milligram per mil.

18 The way it's put together at chairside is
19 that the granules are saturated with the material and
20 so then you're only able to adhere, absorb, as much
21 PDGF that's within that specific solution. Actually
22 the practitioners utilized in the surgical design of

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1 this study, they applied that entire amount of the
2 PDGF to the granules. It is concentration specific.

3 Some of the defects were much larger than
4 others as we looked three dimensionally in terms of
5 the volumetric measurements. Some of the lesions
6 were wrapped around lesions that encompassed the
7 mesial and distal and part of a furcation and so the
8 entire amount was utilized in those studies for
9 comparison. Some of the other dosing and release
10 studies were done by Dr. Hollinger who I think can
11 speak to that point a little bit more if he'd like.

12 CHAIRMAN SUZUKI: While Dr. Hollinger is
13 coming to the podium, Dr. Amar, do you have a
14 comment?

15 DR. AMAR: Did you ever or any of the
16 clinicians come into situations where you had to open
17 a second or third package to be able to feel several
18 sites and how did you manage all this?

19 DR. GIANNONILE: So the study protocol was
20 to treat the target lesion. On average, I think we
21 have the numbers on that, but it averaged about half
22 of the granules which were actually applied with the

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1 platelet derived growth factor. It was never more
2 than one package applied to a lesion.

3 DR. AMAR: Okay. So the question is
4 clinical situation and in clinical setting, and you
5 know that better than me probably, you have a patient
6 coming in your office, upper maxillary region that we
7 open five or six teeth together and they are
8 different lesions. We run out of the material. What
9 do we do? Are we or aren't we allowed to open a
10 second packet and can we graft each one separately
11 when we run out, use another package?

12 DR. GIANNOBLE: I think that what we
13 would do is with that particular formulation of the
14 platelet derived growth factor you would still use it
15 in the same concentration dependent manner applying
16 it to the granules. Then you would treat multiple
17 defects because basically in essence we would need to
18 saturate the particles and then apply them to as many
19 defects that this material could be fit into.

20 So essentially given if there were
21 multiple large defects, then one would open up
22 another package and apply it in the same controlled

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1 manner as what was done in the clinical trial, i.e.
2 there would be the cup. The PDGF would be placed
3 into that, absorbed onto that B-tricalcium phosphate
4 and the delivered into the defect. That would be a
5 way to control for the amount of PDGF on the device
6 itself. Does that address your question?

7 DR. AMAR: I'm still a little bit, I have
8 to be honest, unsettled.

9 DR. LYNCH: I think again we'll have a
10 couple more comments on this.

11 DR. NEVINS: What's important is the
12 concentration. So if you had a cup of the TCP and
13 you had the vial of the liquid, the recombinant PDGF,
14 and you put that in there, now you have a
15 concentration. Let's say what you're describing
16 three lesions in a quadrant. You apply that
17 concentration. That's 0.3. Now you run out of
18 material. You open another package. You have your
19 TCP. You put your liquid in. It's still the same
20 concentration. What you're seeing in the chart is
21 different than what the concentration is.

22 DR. AMAR: I have no problem with that as

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1 long as we label it that it's concentration dependent
2 and we should not mix different preparation together
3 in an attempt to fill larger defects.

4 DR. NEVINS: And we agree with you.

5 DR. RUNNER: This is Dr. Runner. And
6 that's a labeling issue.

7 DR. NEVINS: That's a labeling question.
8 We don't have any disagreement with that.

9 CHAIRMAN SUZUKI: Okay. Any other
10 comment on question no. 1? Okay, Ms. Blackwell.

11 DR. RUNNER: This is Susan Runner. Could
12 we just go ahead and read the question without that
13 way we won't have to keep going back and forth?

14 MS. BLACKWELL: Yes, I was wanting to
15 read them all.

16 DR. RUNNER: Well, let's just do one at a
17 time. Let's go to the second one. Just read it.

18 MS. BLACKWELL: "Endpoints in retrospect
19 of analyses. Please discuss the validity and
20 clinical significance of reliability exclusively on
21 the secondary endpoints and retrospect of analyses
22 identified by the sponsor for approval of this PMA."

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1 CHAIRMAN SUZUKI: Okay. I would like to
2 open this question for panel discussion. Comments?
3 Dr. Cochran.

4 DR. COCHRAN: David Cochran. I think we
5 you know have to consider the light of this trial.
6 The sponsor actually picked the toughest control they
7 could have picked because they picked an active
8 control, if you will. There's a lot of literature
9 available that suggests that pretty most of the bone
10 graft materials that we put in there you're going to
11 get a pretty good response. Some of the literature
12 indicates for Lars Hale, 1997, with the enamel matrix
13 protein 66 percent defect file.

14 If you look in the paper, that was from
15 Greece that was used by the sponsor, in their
16 discussion section, they said that with DFDBA they
17 get 58 to 78 percent fill. So the range for any kind
18 of bone graft material alone is going to be fairly
19 significant.

20 When you use an active control that's
21 going to give you a very positive response, it means
22 the chance to distinguish a difference between adding

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1 some type of protein, the chance of showing that
2 difference is smaller. So given the fact that we
3 have secondary outcome variables that are very much
4 clinically relevant with a bone graft with the x-ray
5 data, I think it's not unreasonable to accept the
6 secondary outcome variables as a proof of concept.

7 CHAIRMAN SUZUKI: Okay. Any other
8 comments from the panel or the sponsor? Question No.
9 3, Ms. Blackwell.

10 MS. BLACKWELL: "Invented use. The
11 sponsor studied GEM-21S and interosseous periodontal
12 defects. In the PMA, the sponsor is requesting
13 approval for the following intended uses: periodontal
14 disease, cystectomy, apioectomy, deficient alveolar
15 ridges, and tooth extraction sites. Are these claims
16 support by the data and the information submitted?"

17 CHAIRMAN SUZUKI: Okay. I would like to
18 open this question for panel discussion. Ms. Howe.

19 MS. HOWE: Elizabeth Howe, Consumer
20 Representative. One of my key interest area has to
21 do with benefit to patients who might have problems
22 with healing, albeit the elderly. There was an

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1 indication that somebody in the population had
2 diabetes. One piece of information I couldn't get my
3 hands on was an Appendix 16-2 that actually wrote
4 down individual subject data.

5 I'm wondering if there is any anecdotal
6 or data information that is available to address this
7 particular population, maybe the elderly in the
8 group. I just saw an summary of age ranges but not
9 necessarily breaking out the people who were 60, 65
10 and over and if, in fact, this could be a great
11 benefit to this particular population.

12 CHAIRMAN SUZUKI: Would the sponsor like
13 to respond?

14 DR. LYNCH: Let me comment from a
15 preclinical data perspective if I could and then I
16 may ask Dr. Lavin to enlighten us as to any
17 stratification that has been done to-date on the
18 different age ranges. But I would like to draw your
19 attention to just the one piece of data, the one
20 site, that we used to illustrate the effects of PDGF
21 in particular in an osteoporotic model, so it would
22 somewhat address the question.

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1 As you may recall from that data, that
2 was in a well-acceptable osteoporosis model where
3 they had removed the ovaries from adult female
4 animals. They become estrogen-deficient and they get
5 osteoporosis very similar to estrogen-deficient,
6 post-menopausal women so it's a very clinical
7 relevant model.

8 In that study, we did demonstrate a
9 strong statistical benefit by addition of PDGF
10 basically throughout the skeleton. The study was
11 done at Mass General Hospital and the investigators
12 looked at both histomorphometry in terms of
13 trabecular bone density as well as quantitative CTs
14 as well as DEXA bone density scans as well as
15 biomechanical strength testing and all of those
16 endpoints and parameters showed a benefit with the
17 addition of the PDGF to again increase bone growth
18 and bone density in an osteoporosis animal model.
19 Dr. Lavin, would you like to speak to any
20 stratification that has been done to date with the
21 different populations?

22 DR. LAVIN: Yes. Philip Lavin. We did

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1 look at age as a stratification variable in multi-
2 variate analyses. Now these were just recently
3 submitted to the FDA so I'm looking at Dr. Runner.
4 She may not want me to go into the specifics of those
5 analyses.

6 DR. RUNNER: The question has been asked.
7 You can respond to it.

8 DR. LAVIN: Okay. Well, in those
9 analyses, we did do cuts of subjects over and under
10 50 and the treatment advantages were very consistent
11 in those over 50 as well as those under 50 for the
12 low dose versus the control.

13 DR. LYNCH: And maybe one final point I
14 could make is again it's not directly the GEM-21S
15 product but certainly Regranex which is recombinant
16 platelet derived growth factor in a topical cream or
17 ointment for treatment of chronic diabetic foot
18 ulcers. It have been FDA approved and therefore, it
19 obviously has been shown to be safe and effective in
20 a chronically diabetic, very severe efficacy diabetic
21 patient and I don't recall the exact data, Dr.
22 Schaumberg is here , but I would suspect that

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1 certainly many of those patients are also elderly.

2 CHAIRMAN SUZUKI: The question I have is
3 with respect to inclusion of tooth extraction sites
4 and perhaps the sponsor can respond. There are many
5 diverse environmental conditions when a tooth is
6 extracted including that of infection which alters
7 the environment in pH sometimes dramatically. Do you
8 have evidence of how your product behaves in such
9 different pH and environmental conditions to be able
10 to justifying including tooth extraction?

11 DR. LYNCH: Maybe I'll -- Maybe I won't
12 sit down here. Sam Lynch.

13 DR. LYNCH: PDGF, in general, if I could
14 use this approach to address your question, Dr.
15 Suzuki, is known as a very stable protein and
16 certainly those panel members and investigators that
17 have worked with it can testify to that. It is very
18 stable, for example, to your point in acidic
19 solutions.

20 In fact, it is the most stable in
21 slightly acidic or even highly acidic environments.
22 For example, many people will store PDGF in one mil

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1 or more acetic acid for a long term of storage
2 conditions. It also appears in the literature to be
3 stable more at least than many other molecules too,
4 for example, proteases, and that may explain some of
5 the benefits of PDGF relative to other tissue growth
6 factors in chronically inflamed environments. Thank
7 you.

8 CHAIRMAN SUZUKI: Thank you. Dr.
9 Cochran.

10 DR. COCHRAN: I think there's a major
11 difference in some of these indications particularly
12 in the last two. My concern is not so much the
13 stability, but the question comes up, "Do you want to
14 stimulate the cells in a tooth extraction site and in
15 deficient alveolar ridge because that's a bone
16 regeneration site and not a PDL?"

17 All the data we've looked at today has
18 been directed towards periodontal ligament
19 regeneration. Periodontal ligament regeneration
20 involves cementum, PDL and bone and the last two are
21 strictly bone sites where PDL is not going to be
22 regenerated. Now I don't know if there's any data

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1 that would support this material in a pure alveolar
2 defect site.

3 And then to comment on the top or the two
4 above of that, cystectomy and apoicoectomy, I'm not
5 sure how the labeling reads for the other devices if
6 those indications were included or not, Susan. I
7 don't know if you remember that or not.

8 CHAIRMAN SUZUKI: Dr. Runner and then Dr.
9 Nevins.

10 DR. RUNNER: I would have to check on the
11 Emdogain and Peptin P-15. However in other 510-K
12 bone filling devices, HAs and bioactive glasses, etc.
13 it's commonly given the range of indications,
14 however, again they are different in that they are
15 specifically bone void fillers.

16 CHAIRMAN SUZUKI: Okay. Dr. Lynch.

17 DR. LYNCH: Sam Lynch, and then I'll turn
18 the podium over to Dr. Nevins. This list of
19 indications was drafted very closely resembling the
20 indications that have already been allowed for β -TCP
21 which is, of course, the matrix used in our product.
22 We don't see any reason why the addition of PDGF

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1 shouldn't limit the labeling beyond what has already
2 been cleared by the Agency for the matrix itself.

3 As we've discussed this morning, PDGF has
4 very beneficial effects on bone cells. It submits a
5 proliferation and came out with great improvement of
6 those bone cells and the revascularization of the
7 site. It's hard to envision from our perspective in
8 a situation where the addition of PDGF would actually
9 be more limiting than the use of labels that have
10 already been approved for β -TCP.

11 DR. COCHRAN: I would make a comment to
12 that. David Cochran. That certainly I'm sure is
13 true. My concern is just that as a panel member
14 without any data in any of the bone-only site that we
15 just don't know what that effect is. So it just
16 makes us a little more uncomfortable when there's no
17 data to support that.

18 CHAIRMAN SUZUKI: Dr. Nevins.

19 DR. NEVINS: Myron Nevins. David, I
20 could only see that the same way. However, if we
21 take the thought process a little bit further, both
22 you and I recognize that the necessity of producing a

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1 periodontion is a more differentiated regeneration
2 than that of producing bone by itself. Where the
3 carrier has the ability to be or has been recognized
4 to be a treatment method, it would seem hard to
5 imagine that this wouldn't do the same.

6 Now what I don't know and I'm unprepared
7 to discuss is what evidence there is that the β -TCP
8 results with the treatment of an extraction mode, but
9 it's very well known in oral surgery we use
10 autogenous bone in extraction sites with relatively
11 little proof. We use allograft. We use xenograft.
12 It's hard to imagine that using the β -TCP together
13 with the PDGF would be any less success than any of
14 them. I understand that there's no study.

15 DR. COCHRAN: It may not be any better
16 either though. That's the thing. It may be you're
17 adding something that's not giving you any benefit at
18 all.

19 DR. NEVINS: But some of the others, I'm
20 not so sure it would give you a benefit.

21 DR. COCHRAN: Right. It think there are
22 people looking at that now.

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1 DR. LYNCH: One maybe further point.

2 CHAIRMAN SUZUKI: This is Dr. Lynch.

3 DR. LYNCH: I'm sorry. Dr. Lynch. Again
4 I'll remind the panel of the data in the osteoporosis
5 animals, clearly a pure bone deficiency, not showing
6 the positive benefit effect of PDGF on simulating
7 bone formation in a pure bone site, if you will.
8 Although not exactly the same, we recognize that
9 there are publications as you are familiar with, I'm
10 sure, showing the use of PDGF in combination with, in
11 that case, insulin-like growth factor for treatment
12 of peri-implant bone defects, again, pure bone
13 defects adjacent to dental implants that were canine
14 studies which also suggested a benefit to the
15 addition of PDGF.

16 CHAIRMAN SUZUKI: Dr. Zuniga.

17 DR. ZUNIGA: Jon Zuniga. When you add
18 the addition of ***1:57:21 in tooth extraction, you
19 are asking to expand the use of this material into
20 sites that I don't think were tested. For instance,
21 when you add those indicators, you could potentially
22 be exposing your material, PDGF, to nervous tissue,

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1 peripheral sinus tissue.

2 If your indication is for cystectomy or
3 you're referring to tooth bearing areas or you're
4 referring to non-tooth bearing areas, including the
5 cranial facial structures, now you could be
6 potentially exposing brain tissue or joint tissue or
7 synovial tissue to the chemical. If you have
8 cystectomy, it's not usual to remove a five
9 centimeter, ten centimeter, cyst and it may not
10 necessarily be odontogenic. It could be neoplastic.

11 So you're exposing a growth factor which
12 differentially accelerates osteoplastic and
13 fibroplastic activity to potentially pathological
14 environments. I think there is a little bit more
15 that's involved especially, I think, when some of the
16 testing, it's not mutagenic or teratogenic, but I
17 believe it was found to be a mild irritant and
18 certainly that material placed against the peripheral
19 or even dura could potentially cause inflammatory
20 processes that we don't know.

21 CHAIRMAN SUZUKI: Do you have a comment?

22 Dr. Lynch.

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1 DR. LYNCH: Just a very brief comment in
2 terms in last point. I believe just a point of
3 clarification that with GEM-21S product, there was no
4 more irritation than in just the TCP alone or any
5 problem with particular graft material. Just another
6 small point is that the Regranex which is used, again
7 recombinant PDGF, for treatment of severe chronic
8 skin wounds involving subcutaneous tissue would
9 potentially also expose the patient to many of the
10 sort of considerations that you were alluding to, for
11 example, the nerve endings and so forth in that area
12 and they have not seen any adverse effects there.

13 DR. ZUNIGA: Jon Zuniga again. It's a
14 significant difference between the end terminal
15 versus the peripheral trunk.

16 DR. LYNCH: Okay. Great.

17 CHAIRMAN SUZUKI: We'll have an open
18 discussion at 3:00 p.m. Comments? Okay, the next
19 question.

20 MS. BLACKWELL: Number four: "Assurance
21 of safety. Does the information submitted by the
22 sponsor provide a reasonable assurance that the

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1 device is safe under the conditions that are used,
2 prescribed, recommended or suggested in the purposed
3 labeling. If the data and the information submitted
4 does not provide reasonable assurances of safety,
5 what information is needed to establish safety for
6 the claimed intended use?"

7 CHAIRMAN SUZUKI: Okay. This question is
8 now open for panel discussion. Any other comments?
9 Okay.

10 MS. BLACKWELL: "Assurance of efficacy.
11 Does the information submitted by the sponsor provide
12 a reasonable assurance that the device is effective
13 under the conditions of used, prescribed, recommended
14 or suggested in the purposed labeling? If the data
15 and information submitted do not provide reasonable
16 assurances of device effectiveness, what information
17 is needed to establish that the device is effective
18 for its intended use?"

19 CHAIRMAN SUZUKI: This questions is now
20 open for panel discussion. Dr. Sharma.

21 DR. SHARMA: Given that the data we have
22 looked at, the effectiveness is established within

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1 each one of the groups. But if we are talking with
2 the labeling and looking at the comparative of this
3 particular device with the control, that is not
4 established. To establish that, one has to be able
5 to design that study and able to prove that in the --
6 hypothesis that we are able to prove our efficacy
7 point.

8 CHAIRMAN SUZUKI: Thank you. Other
9 comments? Dr. Zero.

10 DR. ZERO: Domenick Zero. This is sort
11 of an open question to the sponsors. If you were
12 going to redesign this study, would you choose a
13 different primary endpoint?

14 CHAIRMAN SUZUKI: Dr. Genco.

15 DR. GENCO: I wonder if I could be
16 allowed to give a little bit of a history of
17 periodontal endpoints to answer your question. I
18 remember when pocket depth was the endpoint for
19 periodontal studies and there were some real problems
20 with that because it was so highly dependent upon
21 inflammation.

22 Then we got sophisticated and started

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1 using attachment level because we could measure from
2 a fixed point CEJ or the bottom of the restoration to
3 the apical portion of the pocket appropriate with
4 depth. Then I've seen over the last eight or ten
5 years a move to look at the radiograph assessment.
6 You've heard all the reasons. It's probably a better
7 indicator, not definitive, but a better indicator of
8 regeneration. When you're looking in particular at a
9 regenerative product, it makes sense to look at that.

10 So I see you're plotting sort of the
11 transition of the thinking of the field in terms of
12 endpoints and I mentioned this morning the
13 cardiovascular research that are routinely using
14 composites. So I guess if I wanted to cut down and I
15 came to you next month, I would probably suggest a
16 composite.

17 I don't think that's justification for
18 going back and doing the study over. I think, in
19 your mind, we have a done a composite for you. I
20 think that you'll get the same result if you do the
21 study over except that instead of saying six-month
22 CAL will be the endpoint, it will be a composite or

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1 some other, but it will be the same result. I think
2 it would wasteful. I think you'll be keeping a
3 product from the patients that show clear benefit to
4 require that a new study be done with a new endpoint.

5 DR. ZERO: Well to answer the question,
6 probably a new endpoint would be -- I'm not asking
7 you to do another study at this stage. I'm just
8 asking the question in a hypothetical basis to
9 understand your thinking and then the logic that you
10 were to choose another endpoint how rigorously would
11 that be and how would that hold up in court.

12 DR. GENCO: I think what you would have
13 to do would be the study that you're already
14 suggested. I think Salomon asked the question. What
15 is the correlation between the histologic and the
16 radiographic? I think the data, as a matter of fact
17 we talked about that, is probably there to do that
18 analysis on the 10 or 11 patients that Dr. Nevins
19 talked about to show that there is this correlation.

20 Then you could use the radiographic as a surrogate
21 for regeneration with a little more confidence.

22 DR. ZERO: Domenick Zero. From the

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1 literature you've shared in the application, there
2 are some articles on this subject and again I was
3 learning so I read them. There was a number of
4 statements there that the linear bone height and
5 these other bone fill parameters do not correlate
6 well when you go back and do a reflapping and look at
7 the site.

8 DR. GENCO: Right, I think they are
9 underestimates. They are consistently
10 underestimating, but that's really a different
11 question. If the systematic error is
12 underestimating, it still could be a good surrogate.

13 It's always underestimating by 40 percent, but it's
14 still a good surrogate. If you look from point to
15 point, millimeter to millimeter correlation, you're
16 not going to find it between the flapback measurement
17 of bone, the radiograph and the attachment. You
18 won't find that. But overall, they tend to go in the
19 same direction with the same constant error or
20 difference and I think that's what you'd be looking
21 at.

22 DR. ZERO: If they did that, they would

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1 be well correlated.

2 DR. GENCO: Yes, they are correlated, but
3 they are not one for one correlation. In other
4 words, two millimeters of radiographing does not
5 relate to two millimeters of bone on flapback does
6 not relate to two millimeters of attachment gain.
7 One is less -- The level of sensitivity is the bone
8 would show less. The flapback would show more and
9 the attachment would show even more. But I'm sure
10 there would be a constant relationship among that
11 three and that's what you need for a good overall
12 correlation. These are theoretical. I appreciate
13 your allowing me to answer that question.

14 CHAIRMAN SUZUKI: Thank you, Dr. Genco.

15 DR. SHARMA: I have one other comment.

16 CHAIRMAN SUZUKI: Dr. Sharma.

17 DR. SHARMA: My comment is that you said
18 that you can get the same results if you had a
19 composite endpoint for the next study, but I
20 seriously doubt that it can be exactly the same
21 results because the patient population might be
22 different. There could be several differences.

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1 One of the things I noticed is there
2 were, in the high dose group, more smokers compared
3 to other treatment groups and that may be one of the
4 reasons that efficacy was low compared to other
5 groups. So it's hard to get the same results unless
6 you have exactly the same duplicate thing. It was
7 just a comment.

8 CHAIRMAN SUZUKI: Okay. Dr. Amar.

9 DR. AMAR: I'm just going to make a quick
10 comment. I guess this panel is a little bit hung up
11 on a very

12 DR. STROMBERG: -- was the Chairman of
13 the committee which evaluated PDGF in chronic
14 diabetic ulcers. And we felt that it was important
15 to exclude from incorporation in this labeling
16 patients who had Grade 4 ulcers, which extends down
17 into bone and ligament. The pre-clinical studies
18 again gave us some concern about correct exposure of
19 PDGF to bone, and I will read from the Regrantix
20 package insert which reads, "The effects of
21 Peckopermin which is PDGF on exposed joints, tendons,
22 ligaments, and bone have not been established in

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1 humans. In pre-clinical studies, rats injected at
2 the metatarsal with 3 or 10 micrograms per site
3 approximately 50 to 100 micrograms per kilogram of
4 Veckopermin every day for 13 days displayed
5 microscopic morphological changes of accelerated bone
6 remodeling consisting of periosteal hyperplasia, and
7 sub-periosteal bone resorption and exostosis." I
8 thought this would be useful for you all to hear.

9 CHAIRMAN SUZUKI: Okay. Thank you.

10 Other comments? Dr. Lynch.

11 DR. LYNCH: Sam Lynch. Yes, we
12 considered that part of IDE, the FDA raised that very
13 question and that's part of their review of the IDE.
14 And I think we all felt comfortable that all those
15 issues had been addressed from the five years when
16 the Regrainex was approved in December of '97 to now.
17 And obviously, we've presented a whole wealth of data
18 this morning addressing effects of PDGF on bone.

19 CHAIRMAN SUZUKI: Okay. Thank you, Dr.
20 Lynch. Dr. Runner.

21 DR. RUNNER: I was just going to say that
22 that was how we got them to approve the IDE for use.

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1 CHAIRMAN SUZUKI: Okay. Other comments?
2 Dr. Stromberg.

3 DR. STROMBERG: Well, you must consider
4 that for Regrainex, the safety issue excluded the
5 issue of exposure because the indication excludes
6 Grade 4 diabetic ulcers, so we don't have that
7 exposure-base available to us unless it was
8 prescribed off-label. And in that sense, it's not
9 done within a clinical trial so we don't have any
10 feedback on adverse effects.

11 CHAIRMAN SUZUKI: Okay. Thank you. If
12 there's no other comments at this time, we'll have a
13 15 minute recess.

14 (Whereupon, the proceedings in the above-
15 entitled matter went off the record at 2:13:12 a.m.
16 and went back on the record at 2:19:51 a.m.)

17 (Missed Audio 2:08 - 2:10)

18 DR. SHARMA: You had a composite
19 magnifying for the next study, but I seriously doubt
20 that it can be exactly the same results, because if
21 patient population mechanism, there could be several
22 differences. One of the things I noticed, there were

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1 more smokers compared to other treatment groups, and
2 that may be one of the reasons that the efficacy was
3 low compared to other groups. So it's hard to get
4 the same results unless you have exactly, exactly the
5 same duplicate thing. That was just a comment.

6 CHAIRMAN SUZUKI: Okay. Dr. Amar.

7 DR. AMAR: I'm just going to make a quick
8 comment. I guess this panel is a little bit hung up
9 on very philosophical as well as clinical issue that
10 we all as periodontists have struggled for many
11 years, and I'm still young, but I will struggle
12 probably in the future with it, is that when we look
13 at success, clinical success, and we look at tissue
14 as clinical attachment levels as opposed to how
15 tissue level, is a tooth that is regenerated with say
16 just bone attached, or better bone attached, better
17 in the long term for maintenance, or just clinical
18 attachment levels even at the expense of the long
19 junction apically be more a -- prepared for future
20 recurrence of the disease. And I think that we go
21 back and forth to this issue.

22 I stand at this point, myself, in the

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1 camp of saying that I do believe that a tooth that
2 has regenerated some structure lost as a result of
3 the disease is better prepared for future recurrence.

4 CHAIRMAN SUZUKI: Thank you. Any other
5 comments on Question 5. Ms. Blackwell, are there any
6 additional questions?

7 MS. BLACKWELL: That's all.

8 CHAIRMAN SUZUKI: Dr. Runner.

9 DR. RUNNER: I think Dr. Stromberg wanted
10 to make one clarifying point about the Midlantic
11 Study. There was some comment about exposure to
12 other tissues, and we just wanted to make one comment
13 about Regrainex. And Dr. Stromberg is from our
14 Center for Bio Drug Evaluation and Research.

15 DR. STROMBERG: My name is Kurt
16 Stromberg, and I was the Chairman of the committee
17 which evaluated PDGF in diabetic ulcers. And we felt
18 that it was important to exclude from incorporation
19 in this labeling patients which had Grade 4 ulcers
20 which extends down into bone and in ligament.

21 (Whereupon, the proceedings in the above-
22 entitled matter went off the record at 2:24:33 p.m.)

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1 and went back on the record at 2:30:28 p.m.)

2 CHAIRMAN SUZUKI: Okay. I'd like to call
3 the meeting back to order. We will now hold the
4 second open public hearing session. If there are any
5 individuals wishing to address the panel, please
6 raise your hands and identify yourselves at th is
7 time. Okay. Before we proceed with the panel's
8 recommendations, I'd like to invite the FDA and the
9 sponsor to make brief closing remarks. Dr. Runner.

10 DR. RUNNER: My name is Susan Runner, and
11 I just want to thank you for your input regarding the
12 questions and concerns that we had regarding this
13 application. And I feel that you have answered our
14 questions, and hopefully you'll come to a conclusion.

15 CHAIRMAN SUZUKI: Okay. The sponsor.

16 DR. GENCO: Sam has asked me to make some
17 comments, and I appreciate the opportunity.

18 CHAIRMAN SUZUKI: This is Dr. Genco.

19 DR. GENCO: Dr. Bob Genco. I, too, would
20 like to thank the panel for the excellent questions,
21 and I'm not being patronizing. I think you got to
22 the heart of the issue. These are complex diseases

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1 and treatment is not simple, and experimental designs
2 have to be very creative and very carefully done.

3 I very much appreciate the clinical
4 trialists and statisticians viewpoint, and I think
5 that they have addressed the important issues. They
6 have forced all of us in science to think more
7 carefully about clinical design. In fact, and I've
8 seen clinical trials now for 25 years, they're much
9 more sophisticated and give you much more information
10 than they did 25 years ago. In fact, the whole
11 science of clinical trial design and biostatistics is
12 at a very high and sophisticated level as evidenced
13 by the fact that many institutions now are developing
14 Ph.D. programs in clinical trial design. It's a
15 field unto its own, and it's very important.

16 Having said that, the FDA I think
17 understands that, and I think there's a new era with
18 the FDA, and that era is the interaction with the
19 companies. And I think you're seeing that in this
20 project. You're seeing multiple interactions,
21 multiple meetings, multiple memos and letters going
22 back and forth. And it leads to a complex situation

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1 where one forgets what was pre-authorized, what was
2 prospective, and what was retrospective, so we have
3 made this slide just to address that issue.

4 Our understanding, and I think we've
5 checked with the FDA, that all of the end-points were
6 pre-specified prior to the database lock that are
7 listed here; CAL at three and six months, linear bone
8 growth, percent bone fill, GR due to recession,
9 pocket depth and wound healing in three weeks, and
10 the CAL area under the curve.

11 Now the end-points analyzed -- now those
12 end-points could be considered done before the data
13 blinding was broken, so I think there's certain
14 validity associated with doing those in a blinded
15 fashion on unblinded data.

16 Now look at the end-points analyzed after
17 the database lock, the composite analysis, the meta-
18 analysis. These again were in discussion with the
19 FDA an attempt to interpret, to get some idea of
20 patient benefit. As I mentioned, particularly the
21 composite analysis gives us an idea of the percent of
22 the target population that benefitted from this

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1 treatment. And as we saw using those two composites
2 of CAL and linear bone growth, CAL and bone fill, we
3 came up with 60 to 70 percent of the target
4 population reached our criteria of success which I
5 think were quite rigid. And I remember discussions
6 on the panel sitting where you are, where we had this
7 argument, discussion, animated often - what is
8 clinical significance? I think we have, with the FDA
9 staff, I think have given you hopefully a little
10 insight into a target population which we think is a
11 reasonable representative of the general population.
12 Sixty to seventy percent have actually benefitted
13 from the treatment, so that, in my mind, would argue
14 that this is a clinically significant result.

15 With respect to all of the results, I
16 think you have to look at them en masse too, in total
17 - even though strictly statistically speaking we have
18 defined a primary outcome variable, and you're
19 absolutely right - that is what we should be looking
20 at. However, the reality is the path of biology
21 dictates, particularly for complex diseases, to look
22 more intensely at the data, look at the secondary

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1 outcomes and look at the composite variables. When
2 you do this, you'll see that every single measure is
3 positive, is in the direction of better effect on the
4 patient. The patients are better for having had the
5 treatment.

6 In summary then, as a clinician, and I've
7 seen patients for 37 years, two years less than Dr.
8 Nevins, but still 37 - I am very excited about this
9 product. Yes, I have a connection with the company.

10 It's an area of my research. I have a bias because
11 I've been involved in the research, but I can tell
12 you this is a very effective product. I would use it
13 on my patients, and I hope that it's on the market
14 for future patients. Thank you very much for
15 listening.

16 CHAIRMAN SUZUKI: Okay. Before we
17 proceed with the panel's recommendations, I'd like to
18 invite the FDA and the Executive Secretary, Michael
19 Adjodja, to proceed and give us some background
20 information.

21 MR. ADJODJA: Thank you, Chairman Suzuki.
22 The medical device amendments of the Federal Food,

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1 Drug and Cosmetic Act as amended by the Safe Medical
2 Devices Act of 1990 allows the FDA to obtain a
3 recommendation from an expert advisory panel on
4 designated medical device, pre-market approval
5 applications or PMAs that are filed with the agency.

6 The PMA just stand on its own merits, and
7 your recommendation must be supported by safety and
8 effectiveness data in the application, or by
9 applicable publicly available information. There is
10 reasonable assurance that a device is safe when it
11 can be determined based on valid scientific evidence
12 that the probable benefits to health under the
13 conditions of use outweigh any probable risks. Valid
14 scientific evidence shall adequately demonstrate the
15 absence of a reasonable risk associated with the use
16 of a device under the conditions of use.

17 There's reasonable assurance that a
18 device is effective when it can be determined based
19 on valid scientific evidence that in a significant
20 portion of the target population, the use of a device
21 for its intended uses and conditions of use when
22 accompanied by adequate directions for use and

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1 warnings against unsafe use will provide clinically
2 significant results.

3 Valid scientific evidence includes well-
4 controlled clinical investigations, partially
5 controlled studies, studies and objective trials
6 without matched controls, well-documented case
7 histories by qualified experts, and reports of
8 significant human experience with the marketing
9 device.

10 Your recommendation options for the vote
11 are as follows; approvable if no conditions are
12 attached, approvable with conditions. The panel may
13 recommend that a PMA be found approvable subject to
14 specified conditions, such as position of patient,
15 education, labeling changes, or further analysis of
16 existing data. Prior to voting, all the conditions
17 should be discussed by the panel, or non-approvable.

18 The panel may recommend the PMA is not
19 approvable if the data do not present a reasonable
20 assurance the device is safe, or if reasonable
21 assurance has not been given the device is effective
22 under the conditions of use prescribed, recommended

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1 or suggested in the proposed label. If the vote is
2 for not approvable, the panel should indicate what
3 steps the sponsor may take to make the device
4 approvable. Chairman Suzuki.

5 CHAIRMAN SUZUKI: Okay. Would anyone on
6 the panel like to make a motion?

7 DR. SHARMA: Yes, I'll make a motion.

8 CHAIRMAN SUZUKI: Dr. Sharma.

9 DR. SHARMA: Based on all the data we
10 have seen on safety and efficacy, the device is safe
11 and effective. My condition is that in the labeling
12 we shouldn't have a claim for superiority
13 attributable to this device. I would recommend for
14 approvability.

15 CHAIRMAN SUZUKI: Okay. Is there a
16 second to the motion?

17 SPEAKER: I didn't hear the end of it.
18 Can you repeat it?

19 DR. SHARMA: I will repeat it. The
20 device is safe and effective. The only condition I'm
21 putting is that in the labeling we need to make sure
22 there is no labeling claim for superiority, and we go

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1 ahead and approve this device.

2 CHAIRMAN SUZUKI: Okay. We can discuss
3 this motion if we have a second. We need a second
4 before we can discuss it. And that is a main motion
5 without conditions.

6 DR. SHARMA: That was about the labeling
7 part, that labeling shouldn't have any superiority
8 claims, has to be more like --

9 CHAIRMAN SUZUKI: So is that a motion as
10 a condition?

11 DR. SHARMA: Yes.

12 CHAIRMAN SUZUKI: Okay. His motion was
13 for approval. Can you rephrase your motion first?

14 DR. SHARMA: Sure. The motion is to
15 approve the device as safe and effective device.
16 That's the main motion. And the condition is that we
17 should not have --

18 CHAIRMAN SUZUKI: We don't need the
19 condition at this point.

20 DR. SHARMA: All right.

21 CHAIRMAN SUZUKI: Is there a second to
22 the main motion?

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1 DR. AMAR: I second the motion.

2 CHAIRMAN SUZUKI: Our main motion for
3 approval first. And then we can proceed with the
4 conditions. Is there a discussion on the main
5 motion?

6 DR. COCHRAN: Jon, I think his proposal
7 is approvable with conditions.

8 CHAIRMAN SUZUKI: Okay. Then may I have
9 a condition.

10 DR. SHARMA: The condition is that the
11 labeling should not have any superiority claim.

12 CHAIRMAN SUZUKI: Okay. Is there a
13 second on the condition, that there's no superiority
14 claim.

15 DR. AMAR: I second the motion, but I
16 have other conditions.

17 CHAIRMAN SUZUKI: Okay. We'll vote on
18 this first condition first, and then you can bring up
19 another condition. Is there a discussion of the
20 condition?

21 DR. ZERO: Domenick Zero. Is it
22 necessary to make such a condition? Is the company

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1 asking for superiority claim?

2 CHAIRMAN SUZUKI: Dr. Runner, can you
3 respond?

4 DR. RUNNER: I believe that's a labeling
5 issue. I think you can have that as one of your
6 instructions to FDA in terms of the labeling, so that
7 could be considered a condition, that there would be
8 no superiority claims.

9 CHAIRMAN SUZUKI: Okay. Then let's
10 discuss and vote on this condition first, and then we
11 will go to another condition, if necessary. Ms.
12 Lawton.

13 MS. LAWTON: Alison Lawton. Let me just
14 ask a clarifying question to that. Are you saying no
15 superiority claims on anything, the control that was
16 used in the study, as well as other products? What
17 are you saying as far as superiority?

18 DR. SHARMA: No superiority based on the
19 primary hypothesis, which was that this device is
20 superior to the control in the study.

21 MS. LAWTON: So the CAL end-point only,
22 which was the primary end-point. Is that correct?

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1 DR. SHARMA: Yes, the primary end-point
2 was to look at this device, was for the control
3 device. And it's not about any other device approved
4 or not approved, because that data is secondary data.
5 And that's not from this study.

6 MS. LAWTON: So the superiority claim
7 would relate specifically to the primary end-point of
8 the study.

9 DR. SHARMA: That's right.

10 CHAIRMAN SUZUKI: And there was a second
11 already on this condition. Any other discussion on
12 this condition? Mr. Schechter.

13 MR. SCHECHTER: This is Dan Schechter. I
14 just wanted to point out two things on this. One is
15 the use of the word "retrospective" by the FDA or
16 whomever may have given the impression that this is
17 kind of created analysis afterwards, when in fact
18 these were all pre-defined end-points, and as the
19 sponsor pointed out, these end-points were chosen
20 before the database lock.

21 In addition, if you look at the actual
22 regulation for approving with conditions, it's

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1 contemplated that further analysis of existing data
2 as it's stated on the slide and in the regulation is
3 a reasonable activity for the sponsor to engage in.
4 And, in fact, that's kind of what they've already
5 done. They had existing data, and merely because
6 they didn't meet the primary end-point, at least from
7 some vantage points doesn't necessarily mean the
8 product is not superior in other respects, so I just
9 want to put that on the record for the FDA to
10 consider when this condition is discussed.

11 CHAIRMAN SUZUKI: Okay. Other
12 discussion? If not, I'll call the question on this
13 condition. Each voting panel member will indicate
14 yes, no, or abstain on this motion. There are four
15 eligible voting members at this panel, and the Chair
16 will vote only in the event of a tie. I'll begin
17 with Dr. Amar.

18 DR. AMAR: Yes.

19 CHAIRMAN SUZUKI: Dr. Zero.

20 DR. ZERO: Approval.

21 CHAIRMAN SUZUKI: Only voting on the
22 condition. Dr. Zuniga.

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1 DR. ZUNIGA: Yes.

2 CHAIRMAN SUZUKI: Dr. Sharma.

3 DR. SHARMA: Yes.

4 CHAIRMAN SUZUKI: This condition passes.

5 Dr. Sharma will restate the condition.

6 DR. SHARMA: The condition is that no
7 labeling claim based on the data presented should be
8 made in the labeling for superiority.

9 MS. LAWTON: Relating to the primary end-
10 point is what I thought we agreed specifically,
11 because there are secondary end-point results which I
12 think do show superiority, which were important to
13 have in the label, and so that's why I wanted to
14 clarify that it's the primary end-point we're talking
15 about.

16 CHAIRMAN SUZUKI: Okay. You meant the
17 primary end-point.

18 DR. SHARMA: Primary end-point.

19 CHAIRMAN SUZUKI: That's correct, Ms.
20 Lawton, the primary end-point. Okay. Are there
21 other conditions? Dr. Amar, you had one.

22 DR. AMAR: Yes. I think we discussed

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1 this morning about the concentration dependency and I
2 would like to have on the label - it's a label issue
3 condition - there is concentration dependence or I
4 leave it up to the FDA for better word smith as it
5 would be in terms of concentration dependency, in
6 addition to probably having another condition in
7 light of the Regainex comment related to bone defect.

8

9 CHAIRMAN SUZUKI: Okay. Can you just
10 make one condition at a time?

11 DR. AMAR: Concentration dependency.

12 CHAIRMAN SUZUKI: Okay. That was your
13 motion on concentration dependency. Is there a
14 second before we proceed with discussion? If there
15 is no second, there is no discussion. Then we can
16 have another condition. Okay. That won't be
17 considered as a condition since there is no second.
18 Is there another condition that you'd like to make a
19 motion. Dr. Zuniga.

20 DR. ZUNIGA: My condition would be that
21 the indications for the use be restricted to the
22 treatment of periodontal and/or periodontal-related

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1 disorders. This is based on dental lack of safety
2 regarding interactions with other non-periodontal
3 tissues.

4 CHAIRMAN SUZUKI: Is there a second to
5 this condition?

6 DR. SHARMA: Yes, I will second that.

7 CHAIRMAN SUZUKI: Okay. There is a
8 second to this condition. Is there a discussion on
9 this condition? A labeling issue restricting it
10 primarily to periodontal defects. Is that correct?

11 DR. ZUNIGA: Periodontal or periodontal-
12 related.

13 CHAIRMAN SUZUKI: And periodontal-related
14 defects. Okay. Discussion? Okay. If there's no
15 discussion, each voting member of the panel please
16 indicate a yes, no, or abstention. Dr. Amar.

17 DR. AMAR: Yes.

18 CHAIRMAN SUZUKI: Dr. Zero.

19 DR. ZERO: Yes.

20 CHAIRMAN SUZUKI: Dr. Zuniga.

21 DR. ZUNIGA: Yes.

22 CHAIRMAN SUZUKI: Dr. Sharma.

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1 DR. SHARMA: Yes.

2 CHAIRMAN SUZUKI: Okay. This passes.

3 Any other conditions? Hearing none, we can go back
4 to the main motion, which was Dr. Sharma's approvable
5 with conditions. Is that correct?

6 DR. SHARMA: Correct.

7 CHAIRMAN SUZUKI: Okay. Let's review all
8 the conditions then.

9 MR. ADJODJA: The conditions are no
10 labeling claim of superiority using the primary end-
11 points, and labeling restricted to perio-related
12 defects.

13 CHAIRMAN SUZUKI: So Dr. Sharma's
14 original motion was approvable with conditions. Mr.
15 Adjodja has just reviewed those two conditions, and
16 there was a second to the motion. We can now proceed
17 with each voting member of the panel indicating a
18 yes, no, or abstention. We are now voting on the
19 main motion with conditions. Dr. Amar.

20 DR. AMAR: Yes.

21 CHAIRMAN SUZUKI: Dr. Zero.

22 DR. ZERO: Yes.

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1 CHAIRMAN SUZUKI: Dr. Zuniga.

2 DR. ZUNIGA: Yes.

3 CHAIRMAN SUZUKI: Dr. Sharma.

4 DR. SHARMA: Yes.

5 CHAIRMAN SUZUKI: The motion passes. I'd
6 like to ask if Dr. O'Brien or Dr. Cochran have any
7 additional comments?

8 DR. O'BRIEN: Bill O'Brien. The bone
9 regeneration materials are widely used due to the
10 failure of preventive hygiene and creating
11 periodontal disease. The progression of the
12 periodontal disease can lead to loss of teeth, major
13 problems, and the improvement or the improvement of
14 bone regeneration materials has an important
15 potential impact on periodontal therapy.

16 Since the clinical benefits have been
17 shown to be effective and safe, it appears that this
18 material will be very useful in periodontal practice.

19 I would add one caveat, that watching the technique
20 film or the video, it appears that it was up to the
21 clinical judgment in terms of the application of the
22 TCP, and with other materials the poracity of the

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1 final material, in this case the scaffold, is very
2 dependent on the pressure exerted during the
3 formation of the scaffold, that I would hope that
4 this would be transferred or recommended in the
5 clinical directions.

6 CHAIRMAN SUZUKI: Dr. Cochran.

7 DR. COCHRAN: Yes. I would like to
8 commend the sponsor on an extremely well-designed and
9 executed trial. It was one of the most blinded
10 trials that we've seen come before the panel - well
11 done and well executed, and outstanding. That's in
12 large part due to the outstanding investigators that
13 they used.

14 The proof of principal data, histological
15 data is very solid. I think it's exciting, as Dr.
16 Nevins pointed out, that we see these kinds of
17 histological specimens. I think that's very
18 encouraging.

19 The radiographic data are very
20 convincing, as well, and I think that gives us a lot
21 of excitement to be able to treat our patients. And
22 I think especially, this is noteworthy when you

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1 consider that they used an active control which made
2 the ability to detect any differences quite small.

3 My only concern, I'd like to raise for
4 the FDA, is in the labeling where they have a
5 discussion of the meta-analysis comparison. It's
6 really not a meta-analysis, it's a comparison to
7 meta-analysis data, and I don't feel that that's
8 particularly necessary to be in the labeling or
9 appropriate actually.

10 CHAIRMAN SUZUKI: Thank you, Dr. Cochran.

11 Is that agreeable, Dr. Runner, that that can be a
12 labeling issue.

13 DR. RUNNER: We take all of the comments
14 of the panel into consideration in working out the
15 labeling, yes.

16 CHAIRMAN SUZUKI: Thank you. At this
17 time, I'd like to ask if either the industry
18 representative or the consumer representative have
19 any comments. Mr. Schechter.

20 MR. SCHECHTER: This is Dan Schechter.
21 From information that I've gained from the sponsor
22 and the panel, it seems that this particular study,

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1 it was almost a model of cooperation between the FDA
2 and the sponsor. And, in particular, Dr. Runner and
3 her staff are to be commended for their assistance to
4 the sponsor. And I think other sponsors faced with
5 future studies should not be afraid of coming to the
6 FDA from day one.

7 CHAIRMAN SUZUKI: Okay. Thank you, Mr.
8 Schechter. At this time I'd like to ask the four
9 voting members of the panel to indicate their reasons
10 for their decision, beginning with the first panel
11 member who voted affirmative, Dr. Amar.

12 DR. AMAR: Thank you. I voted for the
13 approval because I believe that this product is as
14 effective as the predicament already in the market.
15 It is safe. In addition to that, the data presented
16 this morning were convincing. They did convince me.

17 The clinical attachment remains the issue, and I've
18 explained that in regard to that particular aspect I
19 think that many products at this point in the market
20 can improve clinical attachment level. What's at
21 stake is the regeneration of the supporting
22 structure, and I think that this product is now

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1 capable of doing that, and that's the reason I voted
2 for the approval; approval for the condition. I'm
3 sorry. With condition.

4 CHAIRMAN SUZUKI: I'd like to next ask
5 Dr. Zero to justify his reason for the decision
6 affirmative.

7 DR. ZERO: My affirmative vote with
8 conditions was based on the strength of the safety
9 data which was very convincing. In regards to the
10 efficacy, I believe that the study, although not
11 satisfying as primary outcome conditions, overall was
12 convincing that there is the potential for
13 regeneration, which was really the prime objective of
14 the study.

15 In addition, there was the ancillary data
16 that was presented from the various animal model
17 systems, and the other clinical data was again in
18 composite very convincing, and swayed my decision for
19 an affirmative vote.

20 CHAIRMAN SUZUKI: Okay. I'd like to next
21 ask Dr. Zuniga for his reasons for affirmative.

22 DR. ZUNIGA: I believe the health and

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1 safety issues were for -- indications for the
2 treatment for using this product were very strong and
3 solid, and based on two FDA approved materials with
4 long history of use.

5 I think the effectiveness data was very
6 well presented and very supportive in the
7 presentations today and the discussions today, which
8 led me to conclude that this will be effective for a
9 very complex disorder that we're still trying to
10 understand.

11 CHAIRMAN SUZUKI: Finally, I'd like to
12 ask Dr. Inder Sharma for his reasons for affirmative.

13 DR. SHARMA: Based on all the data, my
14 recommendation to recommend approval with conditions
15 was based on very safe device, effectiveness even
16 though it was not significant in a comparative way,
17 but there was consistency. There were secondary end-
18 points in the same direction as the primary end-
19 point. And all the data looking at that, I see that
20 it should be made available to patients and they
21 should benefit out of it. Thank you.

22 CHAIRMAN SUZUKI: Okay. Thank you for

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1 your comments. At this time, I'd like to turn the
2 program over to our Executive Secretary, Mr. Adjodja.

3 MR. ADJODJA: Thank you, Chairman Suzuki.

4 I'd like to clarify that the motion just voted for
5 was for approvable with conditions. The following
6 conditions were voted on; that there should be no
7 labeling claim of superiority using the primary end-
8 point, and labeling should be restricted to
9 periodontal-related defects. The vote was 4-0
10 approvable with conditions. Before we adjourn for
11 the day, I'd like to remind the panel members that we
12 are required to return -- they are required to return
13 all the materials that were sent pertaining to the
14 PMA itself. Materials that you have with you may be
15 left at the table, any others that you have may be
16 sent back to FDA as soon as possible. Chairman
17 Suzuki.

18 CHAIRMAN SUZUKI: In closing, I'd like to
19 thank the speakers and members of the panel for their
20 preparation and participation of this meeting. I'd
21 also like to extend a special appreciation to our
22 reviewers, Drs. Amar and Sharma, for leading the

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1 discussion segment of this program, and I'd like to
2 echo Mr. Schechter's comments regarding the
3 partnership of FDA with industry, which is really
4 highlighted I believe in the proceedings today.

5 Since there is no further business, I'd
6 like to adjourn this meeting of the Dental Products
7 Panel. Thank you.

8 (Whereupon, the proceedings in the above-
9 entitled matter went off the record at 3:01 p.m.)