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induces this enzyme in crowded cells. Again, it would be valuable to determine the specificity of these effects by comparison with other cell types.

In sum, this paper shows that increasing concentrations of P-15 stimulate attachment and proliferation of human dermal fibroblasts. In order to show specificity of this particular peptide, it would be necessary to compare these results with a control peptide, perhaps a 15-amino acid peptide with scrambled but identical amino acids. Another possible control is a 15-amino acid fragment of collagen shown in the earlier screening studies to not bind fibroblasts. The defined serum-free conditions of in vitro attachment and proliferation assays are, indeed, valuable for elucidating cellular mechanisms of growth, and these data may suggest utility for in vivo effects. On their own, the data may have limited significance to implants because of the small magnitude of the demonstrated effects in vitro and because of the presence in vivo of serum and multiple cell types. Nevertheless, these studies are of sufficient interest to warrant in vivo testing.

An abstract by Moses et al, entitled, "Synthetic Cell-binding Peptide, P-15, Effect on Human PDL Fibroblast Attachment," did not include quantitative data but stated

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that PDL fibroblasts spread equally rapidly on P-15-containing bovine-derived hydroxyapatite as they did on demineralized bone and on mineral-containing freeze-dried bone, but more rapidly than on untreated hydroxyapatite or other materials including other hydroxyapatites, polymers, coral, and glasses. It is not possible to evaluate these conditions because the data were not submitted. It was only in abstract form.

An unpublished manuscript by Parsons et al. is entitled, "Type 1 Collagen Cell-Binding Analogue Modifies in vivo Response to Hydroxyapatite." Bilateral 8 mm cranial defects were made in 10 rabbits for evaluation of bovine-derived anorganic hydroxyapatite with or without P-15. Rabbits were injected with fluorescent labels at 10 and 14 days just prior to the sacrifice and histomorphometric analysis. The kinetic labeling results were not significantly different, but the static measure of linear bone ingrowth was significantly different,  $p$  equals 0.04. The results were 36.3% plus/minus 12.4 for the hydroxyapatite-filled defects, and 50.9% plus/minus 20.7 for the hydroxyapatite/P-15-filled defects. While the difference between these linear measurements was statistically significant, other measures that were made,

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the percent area of the defect filled with the bone was not different. That was 18.6% plus/minus 3.2 for control HA and 17.7% plus/minus 3.8 for the hydroxyapatite/P-15. Those values suggest that the study was, indeed, designed with sufficient sample size and power to detect differences. It was stated in the text that bone was found around particles of hydroxyapatite with P-15 but not around plain HA towards the center of the defect. We saw some very interesting histological slides earlier this morning. Although there were no quantitative data to support that statement, that observation is of basic interest. The 2-week time point was selected as a window to test for early enhancement of bone repair. This preliminary study appears well designed, but multiple time points, multiple doses of P-15, and comparison with an inactive control peptide would have theoretical benefit. It would be interesting to know whether the 40% difference in linear ingrowth was sustained, and whether meaningful differences in bone area would result at subsequent time points.

That is really what I think was disappointing in this study, that one of the measures, the linear ingrowth of the bone across one diameter within the defect shows statistical significance, whereas, a test of the percent of

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the entire defect as an area failed to show a difference between the two groups.

As pointed out in the manuscript, the rabbit calvarial defect is a useful model to evaluate bone substitute materials. This direct evaluation of the effects of P-15 on HA as a bone-filling material shows a small effect on linear bone ingrowth and no effect on kinetic bone formation or on the area of bone fill.

Recommendation: The sponsor indicates that OsteoGraf/CS-300 acts as a bone augmentation material in two ways. One, the hydroxyapatite component acts as a scaffold for osseous ingrowth and, two, the adsorbed peptide P-15 enhances host cell ingrowth and/or binding.

From the preclinical data provided in the form of articles and abstracts, a number of deficiencies were noted regarding the claims:

First, the in vitro studies do not compare the following: a) binding and proliferation of fibroblasts and osteoblasts; b) binding in the presence and absence of serum; c) binding with P-15 versus a control peptide; and d) analysis of alkaline phosphatase in other cell types bound to the HA particles.

I don't mean to sound like this study is not of

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any value, it is just in regard to the questions at hand with regard to the preclinical evidence of an effect of P-15 on clinical efficacy in periodontal defects. I think we really can't rest too much on these preclinical studies.

Second, there are no detailed in vivo studies showing enhancement of bone growth or repair by P-15.

Third, there are no long-term studies showing the fate of the implant and of reactive bone.

Four, there were no animal data showing efficacy of the P-15-treated HA compared to HA in periodontal defects or defects that serve as a model for the intended clinical application.

I raise this issue because looking at a slow model of repair, such as the cranial defect, there is not a lot of marrow in there. I don't think it really serves as a model for a patient that might have a clinical disorder such as periodontal disease, where there might be inflammation and other tissue and cell types in the defect.

Fifth, the in vivo significance of in vitro binding has not been established. The abstract by Moses et al. raises the concern that the studies do not show a direct relationship between in vitro binding and in vivo osseous ingrowth for OsteoGraf/N-300 and OsteoGraf/CS-300 or the

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other tested materials, such as hydroxyapatite, demineralized bone, freeze-dried bone, polymers or glasses. In other words, the attachment assays are very, very interesting and they tell us a lot about how these cells react to the peptide, but we haven't really seen this as a validated surrogate test for in vivo effects on bone ingrowth.

I was glad we had an opportunity to discuss the issue of migration, and I add this as a sixth item or concern, that migration is a term that could describe the attraction of cells towards a source and that really is the implication I think that that word would have, not only for basic scientists but for clinicians, feeling that a material that was being deposited in the defect somehow attracted the right cells to it.

Today's presentation clarified that the sponsor's report that P-15 peptide promoted the spreading or the movement of cells on the surface of the particles to which the cells have attached. With regard to migration in the in vivo situation, I think the data show an ingrowth of bone, but migration implies I think a cellular process that is not supported by either the in vivo or in vitro studies.

DR. REKOW: Thank you. Are there any questions?

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Dr. Janosky?

DR. JANOSKY: I actually have four or five concerns that probably might be addressed in a session to discuss each of them separately with the sponsor, if that would be an okay format to take.

I am primarily approaching this from a statistical and research design perspective, so I think earlier a statistician from the sponsor had responded to one of the questions.

Let's return to the one question that I raised this morning, that the minimum difference of detection based on the sample size estimation was 1 mm, and also the unreliability was posed with a window of 1 mm and the standard deviation was presented with an estimate of 1.1 mm. If we think about those three things in conjunction, any differences that you see, how could you tease those out from being real differences from error in the measurement system or standard deviation just in the means of measuring?

DR. REKOW: Could you identify yourself please?

DR. YUKNA: I am Ray Yukna. From a clinical standpoint, clinical measurement standpoint in studies of this type, this sort of concordance is actually reasonably good or pretty good -- better than good. The key I think is

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that no difference frequency, which really was the vast majority, 80% and better, up to 90-something percent. The plus/minus 1 mm is what happened and does perhaps relate to your question, but still within the measurement parameters and the use of a pressure sensitive probe, as we do, should have confined the measurements since they were in single units, the unit we were measuring in, to a clinical reality that was reflected in the data. I will turn any other discussion of that over to Dr. Jeffers.

DR. JEFFERS: Good afternoon. I am Barrett Jeffers. A couple of quick things. This morning you were talking about a couple of issues. One is the reliability that Dr. Yukna was just talking about, the way those results were presented. In general, when you see a reliability type analysis, you are looking for, you know, some type of inter- or intra-reliability which could be in the form of a Kappa statistic or something to that effect. Again, the important thing to note here when we are talking about this measurement scale, every measurement is going to be zero, 1 mm, 2 mm, 3 mm etc. That is the detection of the scale here. So, when we are talking about reliability, recall that Dr. Yukna just pointed out that it was between 88% and roughly 90% that had actually no difference in the

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measurement. Okay? So, if you were to convert that over to some type of reliability measurement via a Kappa statistic or whatever you wanted to do, you are going to have pretty high reliability for the measurement. So, again, 88-90% -- rater 1 and rater 2 came up with the exact measurement, the same millimeters so that their difference was zero. Just by looking at that table of numbers, 4-6% had maybe a 1 mm difference and the remaining had a 2 or more millimeter difference. So, the reliability is going to be very high when you have 90% of the data agree exactly. Okay? So, as far as the reliability issue, you know, that would be a response that I would have to that.

The trial was designed to show a 1 mm difference in the OsteoGraf/CS-300 and the standard deviation that was assumed in those original sample size calculations was the 1.1, which is greater than the actual number that you are going to detect. Statistically, any time you see things along those numbers, you know, with a 1 mm difference or greater standard deviation, it points out a couple of things. One is, you know, you might have to use some various statistical methods of analysis in order to more normalize your data, which is what the statisticians at LSU did in their analysis. They used a non-parametric approach

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for determining the differences between the three groups. They also did transformations of the data in order to somewhat reduce that variation that you have.

The other thing that hurts you is that to detect those differences when you have more variability going on, you have to have increased subjects. The sample size calculations that were done, you know, used those numbers, thus, indicating that it would be appropriate for the hypothesis of design, meaning the 1 mm change in OsteoGraf/CS-300.

I think the other part that is going on here is that a lot of the results are stated as OsteoGraf/CS-300 versus the other two groups. Okay? Again, the trial was designed to show that there was a 1 mm difference in the OsteoGraf/CS-300 for that soft tissue measurement. When you are making assumptions or comparisons across those groups, it doesn't mean it is not valid, but it is a secondary type comparison. So, interpretation of those results have to be done at that level. The same point was pointed out earlier by the FDA statistician. So, the statistical comparison between those groups is a valid thing to do. I mean, the way the study was designed with the randomization scheme, all the assumptions are met. But you have to realize that

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it was not what the trial was powered to do. The sample size was for the one group of OsteoGraf/CS-300 with a 1 mm difference, 1.1 in the standard deviation.

One other quick comment, there was some confusion before as well with the equivalence type argument. That is the same type of thing. What we did here, it was not an equivalence trial per se. An equivalence trial shows that two treatments are roughly the same within some error bound. That was not what the original design of this trial was. So when some of the results stated that treatment A, the CS-300, and the other treatments are greater than or equal to or greater than, recall that those are just statistical results that need to be interpreted that way. Okay? It was not an equivalence trial to actually show that treatment B and the test treatment were the same. So, any statement made to that effect was a semantics type error but that was not the type of trial that we had designed here. So.

DR. JANOSKY: Going back to my original question, I will approach it from a different perspective, but since you just ended with the equivalence statement let's take that up since it is fresh on our minds. If I look at the overheads that you have given today, within the clinical hypothesis of the overhead that you just presented, your

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hypothesis was saying that the comparison across these is more effective and/or at least as good as. the trial was not designed to assess this. Am I correct or incorrect?

Then if I go back about five overheads from that, you are making statements about equivalence, again comparing across these three different treatment arms and, again, the study was not designed to assess that. So which data should we pay attention to? Which data should we attend to?

DR. JEFFERS: Again, the study was designed for that 1 mm difference. Okay?

DR. JANOSKY: Within the treatment group.

DR. JEFFERS: Within OsteoGraf/CS-300 --

DR. JANOSKY: Right, exactly.

DR. JEFFERS: -- to show that there was a 1 mm difference, and that is where the original 22 patients came from.

DR. JANOSKY: But you are presenting data that compares them across.

DR. JEFFERS: This is presented from statistical hypotheses that are secondary to what the original sample size calculations were done for.

DR. JANOSKY: With the heading of clinical hypothesis.

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DR. JEFFERS: Correct.

DR. JANOSKY: Right. These are the data that you are presenting to us which, again, was not the study's design.

DR. JEFFERS: Not the study's main, primary hypothesis that it was powered on.

DR. JANOSKY: Right, and all I am doing is looking at copies of your overheads.

DR. JEFFERS: Right.

DR. JANOSKY: In the order in which you presented them to us, with the emphasis on the comparison across those three treatment arms.

DR. JEFFERS: Correct, a statistical comparison which is, again, secondary and it wasn't necessarily powered for that comparison but the design of the trial allowed those types of comparisons to be done with the randomization scheme etc. So, statistically they are valid comparisons across.

DR. JANOSKY: I would differ with that. If I remember your sample size estimations, they were done within a group looking at a 1 mm difference with that standard deviation of 1.1.

DR. JEFFERS: Sure.

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DR. JANOSKY: That sample size estimation was based on a sample size for each of the groups.

DR. JEFFERS: Right.

DR. JANOSKY: And you are using that collectively as a sample size. That is a very different and important specification.

DR. JEFFERS: Sure. As far as sample size and power to detect differences --

DR. JANOSKY: That is right.

DR. JEFFERS: -- but if you look at just how the design is done, and the randomization scheme etc., it doesn't mean comparisons can't be made, and there is nothing to be made from those comparisons --

DR. JANOSKY: Comparisons being made as secondary, not presenting them to us as primary clinical hypotheses..

DR. JEFFERS: Right.

DR. JANOSKY: Which is what this presentation is giving us.

DR. JEFFERS: But they are secondary, correct.

DR. JANOSKY: But, again, you are not presenting them to us, or they have not been today presented in this way.

DR. YUKNA: Can I make a couple of comments?

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Number one, when I presented the material I emphasize the intra-patient differences from pretreatment to post-treatment at the different time periods. That really was, you know, one of the main focuses. In addition, the power analysis was originally done both ways for the intra-patient differences as well as across treatment differences. So, since we needed to have the controls we wanted to make sure that it was appropriate for both. So, the power analysis was actually established on both of those.

DR. JANOSKY: But your only primary hypothesis was a comparison within a group, pre to 6 months. Is that not correct?

DR. YUKNA: Well, I really don't know how to answer that. I mean, yes, and other things were evaluated as well. I mean, you know, if that is the case, yes, and we showed that I think. But there were other data that became available that we felt strengthened the clinical utility of the material in its presentation and we included all those things.

DR. JANOSKY: Let's leave this point again. Maybe we will have to come back to it a little bit. If I look at the comparisons across the three centers, I have seen

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something, not in what I have with me today but in the other supporting documentation, that there was comparability across the three centers, and that was also a question that was brought up by one of the Panel members today. I have lost track, unfortunately, of who that was. You weren't powered to do that comparison. So, when you find no differences across those centers can we truly conclude that there were no differences across those centers?

DR. JEFFERS: As with any of these types of tests, to positively conclude that there are no differences or that there are no treatment differences or anything else, you know, we cannot do. Obviously, it is not an equivalence trial design where you need a lot more centers or patients within each center to actually prove those hypotheses. But from the clinical significance and statistical significance level, looking at the data, there were no differences.

DR. JANOSKY: But my concern is that you didn't have the power to pick up those differences even if they were there. That relates to -- please help me; I can't see the first letter -- Dr. Glowacki -- I think she had mentioned about an age effect perhaps earlier as to site differences and what about the age effect, and were there age effect differences and, again, you weren't powered to do

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that, to look at those differences.

DR. JEFFERS: Right, it wasn't powered to look at those differences, yet, they were allowed for in the analysis via the site --

DR. JANOSKY: But my point is that if you didn't have the power and you found no effects, which you say you did, then is it just due to low power that you didn't find effects? You have no way of knowing.

DR. JEFFERS: Right.

DR. YUKNA: The only other way of knowing is historically in the periodontal literature. There is no evidence that the age of the patient has any real effect on the results of this type of treatment, in any study.

DR. JANOSKY: Age, but then the site issue is what I am concerned about also.

DR. YUKNA: Treatment site?

DR. JANOSKY: Comparability across sites, exactly. Let's sort of go into a different realm and maybe I will turn the floor over to someone else for a while. Let's talk about the data analyses for a second. The sample size estimations, I am assuming, were based on a parametric test. Is that correct?

DR. JEFFERS: Yes, from my recollection. I did

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not do those; more of a review after everything had pretty much been done. From my review, that is true.

DR. JANOSKY: The data were analyzed both using a parametric and a non-parametric approach. I have seen that numerous times in here. If I look at the data in which they are presented, this one chart you gave us in terms of quintiles, clinical study by percent defect fill by quintile. This sort of clues me in as to why perhaps you used non-parametric as well as parametric. Can you speak a little bit to that, please? If I see the test situation, it looks like you are definitely in a positively skewed distribution. The negative control is definitely -- excuse me, negatively distributed distribution. If I look at your negative control, it looks like a positively skewed distribution with the positive control being a symmetrical or bimodal distribution. Going into the sample size estimation, these distributional shapes were not taken into account. I am looking at this overhead that you presented to us today.

DR. YUKNA: Let me answer that. This was not intended as a primary method of analysis. Once the data was accumulated and it seemed like there was such a definitive trend towards the effectiveness of the CS-300, we looked at

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the data in a variety of different ways, and I didn't mean to confuse anybody by trying to present not just mean values but perspectives on what the effect of the treatment was from a clinical perspective. So, this was simply just a pattern of the results without any statistical tests being intended or done.

DR. JANOSKY: That is not why I am bringing it up.

DR. YUKNA: Okay.

DR. JANOSKY: I am bringing it up because it lets me know what those distributional shapes are. I don't have any plots to actually see the outcomes so I am using this to give me an estimate as to what that distributional shape might look like. I understand that you didn't use these values exactly for analyses. These let me know that these are not symmetrical distributions. So then non-parametric tests were most likely warranted.

DR. JEFFERS: Right. Again, with a sample size of 30 you are getting on that borderline of, you know, even not having the non-symmetrical distributions and some of the parametric statistical tests will give very close results to the non-parametric.

DR. JANOSKY: But this speaks to the issue of whether you had an adequate sample size or not because the

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sample size estimations were based on parametric tests, not non-parametric tests, and the data seem to suggest that non-parametric tests are warranted.

DR. JEFFERS: Granted, the distributions aren't normally distributed by looking -- again, you know, I haven't seen all the data, but this is not normally distributed data but, again, the analytical methods when both were done agreed. The parametric and non-parametric tests that they performed on this data virtually agreed to multiple decimal places. So, with that type of agreement between the two you can easily jump on one side or the other and start arguing the non-parametric stuff but it always kind of comes back to the fact that in general these parametric procedures performed very well even in cases when they were not intended, and you do have some type of skewed distribution. You know, I believe that is the case here and it is not, you know, a big issue that the sample size calculation was done with the parametric assumptions, whereas the analysis was done via non-parametric tests or parametric tests. I don't feel personally that that is going to skew any of this.

DR. YUKNA: If I may also add, it is reported in both ways because many of our periodontal journals ask for

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that, or if you send it one way they ask for it the opposite way. I have to take the blame for having both tests kind of recorded as being done, and they did agree almost perfectly. So, both are reported that way but, as Dr. Jeffers said, they agreed almost exactly anyway.

DR. JANOSKY: I think it is good practice, clearly, when we look at this distribution to report both of them. The issue I am concerned about is that sample size estimation.

This will be the last one. You have my word on it this time. How about that?! Your post hoc tests following up from either the Newman-Coles procedure -- I am assuming that that is a repeated measurement analysis of variance, even though it does not state that it is a repeated measures analysis of variance. It stated pretty much in all of the reporting and all of the tables that those were non-controlled post hoc. Most of the time they are actually reported as paired t-tests. So, the standard practice is to control the alpha when you are doing post hoc testing, or to control the alpha  $V$  in planned testing.

DR. JEFFERS: Right.

DR. JANOSKY: Was it done and it just was viewed as an oversight and not presented, or what was the reason

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that it wasn't done etc.?

DR. YUKNA: I will address that. This was done with a computer program and that is the way the computer spit it out. Whether they took into account those things, I don't know. The only repeat measures applications are from pre to post-treatment within a treatment group. Across treatment groups it was not repeat measures because those don't apply. So, I can't really answer that, except that this is the printout that we got so I presume that they accounted for this.

DR. REKOW: So I will open it for discussion. We have a number of questions posed and probably a number of issues that could be addressed. Are there particular things that you, as a Panel, want to begin with? We will start with Mark Patters.

DR. PATTERS: If I understand this correctly, you submitted this material originally to FDA as a 510(k), and FDA came back to you and said, because you incorporated this 15-amino acid sequence linear peptide, that there is no appropriate predicate device to base a 510(k) on and you have to submit this as a PMA. Am I correct in that?

DR. TOFE: Yes.

DR. PATTERS: So, therefore, in my mind the reason

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we are here today is because you put this peptide on your hydroxyapatite. Had you not done that, you would have had an approved 51(k) already on the material. So it seems to me it is incumbent upon you then to establish in additional studies the utility of this peptide.

Now, quite clearly, it was pointed out in some of the materials that I have read that trying to incorporate an additional parameter, such as the N-300, in the existing clinical trial would require patients that required four bone grafts, which is really unreasonable, and I completely agree. You would still be looking for patients that met that criterion.

On the other hand, FDA does not ask you necessarily to submit only one study and certainly other studies could have been designed to ask that very question. I personally feel that it is incumbent upon you to provide the FDA and the Panel with this information given that it is the whole basis for the need for a PMA. So, that is where I am coming from.

DR. REKOW: Dr. Amar, did you have something?

DR. AMAR: There was some concern raised earlier, and I read the material and the documentation, with the shelf life of the material. Has anything been done in terms

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of that. I understand that the accelerated aging studies are under way. If the sponsor could inform us as to what the shelf life would be?

DR. TOFE: The shelf life studies are completed and validated, and a three-year shelf life has been documented. Three years.

DR. REKOW: Mr. Larson?

MR. LARSON: Just a comment that there is a lot of focus here on the issue of the P-15, and I can understand that focus from a scientific basis and, indeed, even from a clinical basis. I am not quite sure of the answer to this dilemma but I want to bring us back to the regulatory purpose of our being here, and that is to judge the safety and effectiveness of the device as submitted. The fact that OsteoGraf/N exists should not be particularly important to that decision. If this device were submitted as this combination of HA and P-15 and OsteoGraf/N didn't exist would our thinking be different? It might not, but I just want to come back to that regulatory issue of safety, which I believe we pretty much can see is the case, and effectiveness, and then the question of how effectiveness is evaluated.

Then, of course, there is the issue of the

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labeling and claims, and that is the other area of concern. But for the primary question maybe we need to refocus a little bit.

DR. TENENBAUM: Again, I do compliment you on the design of the study but I still find that, irrespective of whether OsteoGraf/N existed before or not, as a clinical scientist I would still look at this as a vehicle carrying P-15 and, therefore, I would ask the question what is the P-15? What is this biological agent that is supposed to have biological activity doing on this vehicle and what would happen with vehicle, i.e., HA alone? So, one could suggest, although I think it is very unlikely, what if P-15 inhibited healing versus OsteoGraf/N because it attracted fibroblasts or something like that rather than osteoblasts?

So, that is still something that I find of concern, that we are talking about a material with a putative biologically active agent and, yet, we do not know how that is contributing or if it is contributing in a positive or negative fashion to healing. So, I still feel it is important somehow to address that fourth arm, as it were. I agree 100 percent that you couldn't do it in single patients with more sites, and I think that this is a well executed study to initially show that OsteoGraf/CS has the

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effects that you have demonstrated but you still have to ask the question, I think, how it would compare to the vehicle alone.

DR. YUKNA: Well, it is certainly doable. It is a question of practicality and clinical utility. But I presented in one of my first slides, the historical precedent for HA studies in which the routine defect fill is about 50% and, you know, the attachment level gain is relatively minimal, and the HA and the OsteoGraf/N is not likely to perform any differently than those other HA studies in periodontal defect.

Again, having been in this area of research about 25 years, this stands head and shoulders above consistent defect response over any of the materials, including several different brands of HA that I have evaluated in similar situations in the past. So I agree with you that on a head-on, one-to-one basis that has not been done, but from the 12 or 13 studies that were included that did HA previously, there is certainly a dramatic difference.

(Slide)

DR. TOFE: The question of OsteoGraf/N keeps coming up and I am a strong believe in what the market tells you. We engaged Harbor and Associates to do some market

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research for us, looking at periodontal surgery and grafting materials, specifically to try and quantify and give us a clue about what type of numbers of flap procedures are done in a clinical practice out there. What they did was, in essence, for the year 1996, they gave us a report that basically said that in 1996 there was approximately 1.4, 1.36 million osseous surgeries and graft procedures.

Then they did the next step and they broke it down to try and differentiate between the number of flap procedures that had a graft material and the number that didn't. As we can see, obviously, as Dr. Yukna pointed out, without graft under surgical debridement it was 54%. So, the negative control is debridement, the standard procedure which is utilized by the clinical community. The grafts, as a whole, represented 45%.

If we broke that down further, which we didn't in the study, we saw the next largest group and that is allografts representing 264,000. In other words, the practice, the clinical utility was related to our positive control and our negative control.

As I said, the market dictates the utilization of materials. And you can see with the OsteoGraf/N, though I must admit it was surprising to me, there was only 21,000 or

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1.6% procedures of all the flap procedures that had been utilizing just the "N" natural matrix. That was it. The clinical utility and how to deal with what is out there being used out there in the clinical community is debridement and allografts.

DR. PATTERS: Would you be adverse to a post-approval study to answer that very question?

DR. TOFE: No, I would not. I think it is an academic question though because, like I said, the reality is -- I hoped that the preclinical data had answered the question of were we looking at an effect of the matrix, for lack of a better word. I think Dr. Larson's comment is correct. You know, we seem to be focusing on the N. But if we were looking at this simple component for the inorganic and component for the organic irrespective of that, the data would speak for itself. But from a scientist's point of view, absolutely not, but from clinical utility it doesn't really make much sense.

DR. REKOW: Dr. Jordan?

DR. JORDAN: I am trying to understand your rationale on this slide. Please don't move it. Correct me, I am hearing you say that OsteoGraf/N wasn't used because of its not being used very much.

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DR. TOFE: Yes, I don't know why it is not being used.

DR. JORDAN: Okay, that is what you are saying.

DR. TOFE: Yes.

DR. JORDAN: But, now, isn't the peptide being used? To me, if that is the case then why would you use it? You are giving me an argument to not have this product because you are using this product with this very unutilized one. I don't understand.

DR. TOFE: No, what happens is that the peptide product is obviously not on the market today.

DR. JORDAN: Right.

DR. TOFE: This is just the matrix. What we are trying to establish is that the matrix is a matrix, and the peptide added to the matrix takes it from over here to, hopefully, having some clinical utility in the same arena as the freeze-dried bone. But itself, it is over here. But with the presence of the peptide it is more up here where allografts are being utilized.

DR. JORDAN: Based on what?

DR. TOFE: Basically what I am saying is that the matrix itself, the OsteoGraf/N is just a particulate material. It has limited utilization in flap procedures as

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it is today in the marketplace. The majority use is debridement, the negative control, or the allograft. Those are the materials which are utilized because the clinical community obviously feels that they are either effective or the allografts don't do much and debridement is fine.

DR. YUKNA: Well, the other point to that is that OsteoGraf is an HA and all of the HAs are sort of classified together and probably act the same, as I tried to address to Dr. Tenenbaum's question, and the clinical results with those have not been as good as some of the other materials, the allograft etc. So, the choice of clinicians today would not be towards a plain HA material just because the literature and the trend seems to be towards the allograft which theoretically has BMP that it releases in these wonderful concentrations and great things happen, which has not been proven yet at all in the human periodontal defects, except for one study. So the usage reflects the fact that it is a plain HA. If you can add something to that that would change the body's reaction to that material and improve the clinical results, then that is sort of the product that we tested clinically and the company developed. So the OsteoGraf/N -- it could have been -- I don't know, CalciTech HA or whatever probably, and the peptide could

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have stuck to that just as well and been used as a product as well.

DR. JORDAN: You brought up the issue of the market. So, if I take from that argument that you are now going back to the market and saying we have improved OsteoGraf/N but we haven't compared it --

DR. TOFE: We aren't saying we have improved OsteoGraf/N. OsteoGraf/N doesn't exist. We are talking about OsteoGraf/CS, which happens to have a calcium phosphate matrix, which happens to be a xenograft. We have a matrix that we have a lot of experience with which is simply a matrix. Forget the name, a matrix to which we added the P-15. That product is the OsteoGraf/CS. The other product, the N, is out there but the clinical community has determined that HA per se, as Dr. Yukna said, whether it be this, that or whatever, is just not overly effective in that particular indication. When you do a flap procedure, obviously you are putting in some type of a graft material. Am I answering your question?

DR. JORDAN: No. I am not sure and I don't want to belabor the point but, again, I am going from the perspective that you introduced, in terms of the market -- you brought in the issue of the market and if I go from that

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perspective, from the market, and you are now going to present this from that perspective I still don't understand your rationale for the new product being any better since you are comparing it to this. Why would a dentist want to use this product as opposed to OsteoGraf/N? I mean, you haven't compared the two.

MR. LARSON: May I just make a brief comment?

DR. REKOW: Go ahead.

MR. LARSON: As I see it, the company is bringing before us this product which is an HA matrix with P-15 on it, and that really has to be our focus. So, while I recognize scientifically that, yes, we do want to see the other information, and maybe postmarket surveillance is the way to do it or a postmarket study, but the device is the combination. That is it.

DR. REKOW: Dr. Trummel had a comment.

DR. TRUMMEL: Is it safe to assume that you believe that OsteoGraf/N-300 was not different than any other HA out there on the market and, therefore, you would assume that the historical HA performance was what one would see if you, in fact, tested OsteoGraf/N-300?

DR. YUKNA: From a clinical standpoint, probably yes. That has been shown with variations on the HA theme

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--porous, non-porous, resorbable, non-resorbable, whatever.

DR. TRUMMEL: So there was nothing particularly unique about OsteoGraf/N-300 from CalciTech --

DR. YUKNA: It is a xenograft rather than being an alloplast, but basically the chemical makeup of it and everything else is the same. You know, our first evolution of the synthetic graft material was about 15 or 16 years ago. Now we have the allografts which have always been around. We have glasses and we have other proteins, and we have developments of improvements in some of the basic things we tried initially and, to me, this is another improvement. But I think the reaction in the periodontal environment, in the periodontal defect, would be, I would venture to bet, the same as any other HAs.

DR. STEPHENS: There are a couple of things that bother me. One of the things is that the small amount of sales of the OsteoGraf/N seems to be used as the reason for -- it seems to me that the small amount of sales is being used to justify the fact that it doesn't work well, and it seems to me that that is being done without us really knowing what the scientific performance of the material is.

The other thing is that I am not sure that it makes sense to lump the performance of all HAs together, and

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I suspect that if you had HA manufacturers in the room they would take exception to that, lumping porous and non-porous, and I think that even other manufacturers of bovine-derived HAs with different proprietary processes would probably take exception to that. So, I think that putting them all together and using the combined performance of HAs is not helpful to us here.

DR. REKOW: If I can take the Chair's prerogative though, I think that the comparison that needs to be made is, is it better than -- no, that is not true. Is this material safe and is this material effective in treating adult periodontitis. Whether or not it is better, the same or different, does this stuff work and is it safe is the real bottom-line question that we need to address. Dr. Jordan?

DR. JORDAN: That is a good question. In terms of the number of people who were studied, my question is, is 31 a sufficient number to be able to, on a statistical basis, give an answer to that and, again, is there a need to have this gender and ethnically studied as well to be able to give an answer to that, as well as age-wise? We have 31 people. For me, 31 is an extremely small number to be basing this number on, period. So I would need help from

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industry, the Panel or the FDA in terms of this, if that number, 31, sufficient. Can you take one person who is 71 and then market the whole country based on that? Are we comfortable with that number, and does that one person represent -- do we need more? Is there a need for gender, ethnic etc. studies?

DR. JANOSKY: Probably about 30% of the questions that I was bringing up today actually were trying to get at whether that sample size estimate was appropriate or not appropriate. Based on the responses I got from the sponsor, I am still not convinced that that a priori derived sample size estimate, given the results that they found, was adequate. So that would be my bottom line unless perhaps there is some other information that would be helpful at this moment.

DR. REKOW: Would the sponsor respond to that?

DR. YUKNA: The comment has to be that we had input from the FDA from the very beginning and were approved for an "n" of 22 to accomplish the study. We discussed it with them. The "n" was increased to account for dropouts and, in fact, we were allowed up to 40. So we ended up with 30 patients which was satisfactory for us to even begin the clinical protocol. Now, after the fact to come and say that

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wasn't what we really meant or what we really intended is sort of improper.

The other thing is that this is not a drug study per se; it is a device study and in the periodontal environment, periodontal studies, this number of patients for an internally controlled, self-treated, 3-arm study is twice as many as any other study in the literature. Even the recently approved Emdogain had slightly less number of patients in their clinical study. So we feel that, yes, gender was equally distributed. The age distribution was given just if there was a question that everybody was in the younger age group. Adult periodontitis is above 35 years old. As I said earlier this morning, in our literature there really is no appreciable difference or detectable difference in healing response over time for these types of procedures in younger and older individuals. So, every way we looked at it, every piece of advice we got, for this type of study to evaluate a device in periodontal defects this was a most appropriate number of subjects, a most appropriate sample size and most appropriate study population for the indications that are claimed, which is strictly adult periodontitis.

DR. JANOSKY: If we go through sample size

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estimation procedures, just to sort of remember what we all know, we go forward with a lot of estimates. Things aren't certain, because if they were why would we do the study? So, we go forward with a lot of estimates. Then sometimes we do interim analyses; sometimes we do interim sample size estimations to see whether those estimates were on target or not on target. So, the issue I would raise to you and the question I would pose is if you think about those original estimates and now where you are, how far off were you? Then, what impact would that have on sample size estimation?

Issue one, reliability: the sample size estimation presumed that you had 100% accurate reliability.

Irrespective of which estimate we use, we know that you had less than 100%, which is acceptable in some realms but what impact does that have on sample size estimation?

Issue number two, what hypothesis was being investigated? And that was within your test not across the test.

Issue number three, what was the standard deviation? And if I look at the estimates for the standard deviations of what you obtained, were they realistic with the 1.1?

Issue number four -- and I am losing track so it

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might be issue number five -- looking at what statistical tests were used and whether they were appropriate or not?

So, if you could address that issue that probably would be a best approach. Given all of those estimates, how far off were you, and what impact would they potentially have on that a priori sample size estimation?

DR. YUKNA: The standard deviations in the clinical measurements we made were a little bit greater than what we presumed. My understanding is that if the sample size was not sufficient we would not have shown the statistically significant change within treatments particularly. So, the fact that we did kind of establishes that the "n" was satisfactory, in my understanding of this. Dr. Jeffers may add to that. I personally feel very comfortable with the way the study was done, with the sample size and the distribution of patients, age, gender, consistency across treatment centers, etc.

DR. JANOSKY: Along with that is that issue of generalizability which was just raised in terms of distribution of patients typically seen, in terms of age, in terms of gender, in terms of race, whatever it might be. You didn't do random sampling. You did random assignment of the treatment conditions in terms of order, but clearly,

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given the research study, you couldn't do random sampling which would assure you generalizability to the population. So, could you address that issue? Was that sample size estimate appropriate for generalizability of the results to the patient pool? We are talking about a million or so patients -- I forget the numbers -- that are out there that could possibly be treated. So, that is the other issue of sample size estimation, the generalizability of the findings.

DR. YUKNA: Again, I will repeat that I think that given the nature of the patients that were treated and that they were selected because they met certain criteria to get into the study as far as disease state and other factors, the distribution of age, gender, anything you want, the depth of the defects and everything else, to me, makes it generalizable. I personally, clinically, ethically and professionally do not have a problem with these numbers compared to what we have based a lot of our treatment on in the past. I mean, they are head and shoulders above that as far as the numbers of patients, the consistency of the study and the distribution of patients, distribution of defects, etc. So, I am sorry if I can't answer any better than that.

DR. TOFE: With all due respect, we have the two

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LSU statisticians, we have our own contract statistician and we have the FDA statistician, in fact, just recently we have had a statistician from the American Academy of Periodontics, who reviewed the manuscripts, all agreeing with the approach, for lack, of a better word. I understand your concern but I don't know where to go.

DR. JANOSKY: If I read through the letter from the FDA statistician I might come up with a different conclusion than you just did though.

DR. REKOW: Are there any other concerns or questions that the Panel has?

(No response)

There are two other questions that were raised by Dr. Betz, and I was in error before, the latest version of the questions is the one that has FDA on the front that is in your package.

One that we sort of hinted at, and I want to make sure that all the conversation has been finished, is whether or not the stated presence of P-15 establishes a claim, whether implied or direct, of clinical utility and clinical effectiveness for this device. It is probably the effectiveness issue that should take precedence. Is there more discussion that needs to be had on that, or has the

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Panel pretty much figured out their opinion of these things?

DR. TRUMMEL: I have a question, if I may, about that procedure.

DR. REKOW: Yes, please.

DR. TRUMMEL: Is the Panel going to vote on each one of these six questions, or how is this going to be resolved?

MS. SCOTT: The Panel questions are offered for Panel discussion to assist FDA in addressing these issues. Then after the Panel has discussed and provided recommendations regarding the questions, then the Panel will actually take the vote on whether or not they believe the PMA is approvable or approvable with conditions, and so forth. When we get to that point I will read a full statement on options that the Panel has in terms of voting regarding the PMA.

DR. REKOW: I just heard those words and I am not sure that I understood the answer. You want us to make a recommendation on each of these questions? Okay. So, we will go to number one, which is one that we really have not addressed in very much detail. Does the name "CS" for cell stimulating constitute a device claim? Can I hear some words and recommendations?

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DR. PATTERS: I have heard you say, Dr. Tofe, that "CS" stood for cell stickiness, then I thought cell stimulating but I haven't seen it in your written materials anywhere.

DR. TOFE: And you are correct.

DR. PATTERS: I have a car that says "LXI" on the back but I don't know what it means. It is just a designation. Is this a designation or does it mean something?

DR. TOFE: I have had six years of Latin, and what "CS" means is "cytostagin" and that basically came up one night after having a number of beers with Dr. Bhatnagar. That means cell sticking. That is what "CS" means. It was always meant to be "cytostagin," which means cell sticking. When we talk about cell stimulation, it was the definition we gave before -- attraction, migration, differentiation. You have seen in the actual PMA that we used the word cellular activity. It is semantics.

DR. PATTERS: Did you have a particular fondness for those two letters, or could we take some other two?

DR. TOFE: I don't know.

DR. REKOW: Are you using "CS" simply as the letters or are you using the words in any of your

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literature?

DR. TOFE: No place in the labeling or anywhere are the words mentioned cell stimulation. In the actual indication and no place in the labeling do we make this -- I can understand the concern about a claim of cell stimulation. There is nothing in the labeling whatsoever. CS, unfortunately --

DR. REKOW: It is like the "LXI" is that what you are saying?

DR. TOFE: It is just because of the cell sticking.

DR. STEPHENS: What does the "N" in N-300 mean?

DR. TOFE: The "N" in N-300 means natural, meaning naturally-derived material. What we tried to do for the clinical community -- like, example what I showed you on that pinwheel, we have D for dense material; we have LD for low density. We tried to get some simplistic way so that clinicians would have less difficulty understanding the various types of options.

DR. PATTERS: One more point, Dr. Tofe, you wouldn't put the approval or disapproval of your product on those two letters, would you?

DR. TOFE: No.

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DR. PATTERS: You are flexible on those?

DR. TOFE: Yes.

DR. PATTERS: That is what I thought. Thank you.

DR. GLOWACKI: I think the semantic issues are really a part of all of this because I am quite willing to accept the fact that the clinical study was designed to determine whether CS-300 was as effective as demineralized banked-bone is in treating periodontal defects. However, there is the notion here that the P-15 adds something to the ceramic apatite, and I think that is where we are getting into some discussion about what is the comparison. To say that it enhances cell growth or cell attachment and, therefore, ingrowth of bone and treatment of a periodontal defect is, for me, the basis of the confusion about what the claims are. To me, cell stimulating, cell stickiness, enhanced cell attachment are all device claims.

DR. AMAR: I am putting myself into the shoes of a periodontist although I am a little bit of a periodontist, and explaining and trying to do a bone grafting for a patient and explaining all the options, and coming to the patient and saying we have DFDBA, we have this and that, and this material, and the patient comes back and says, "what is inside of this material?" It is the dentist or the

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periodontist who is in charge of explaining the label in this particular event and not the patient understanding what is inside. What is the periodontist supposed to say to the patient?

DR. YUKNA: Patients ask us all about that, as you know. "Is the bone safe? What is in it? What is it made of?" My answer would be that it is a basic bone-like material; has the same chemicals of bone, to which a small synthetic material has been added that appears to have some positive effect, and given the other choices that we have it would be my recommendation that this is what we use. It appears to be completely safe and it seems to be at least as effective as the other things that we would have on the market, with the potential that it may be better. That would be my explanation.

DR. AMAR: And, again, this is just because of the labeling of P-15, a synthetic peptide, that in fairness of the patients we have to disclose something to.

DR. YUKNA: I agree. I disclose everything. Our consent form at the school and privately says that because we have a lot of patients that might not like the nature of the bovine, or might not like the porcine derivative of the bone, we have to disclose the source of the material and

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what is in it. That is a given in any good clinical practice consent form or patient-doctor interaction.

DR. AMAR: I am still a little confused as to what we need to disclose to the patient in terms of "CS" or P-15 or anything like that.

DR. YUKNA: I gave you how I would explain it to a patient. I think every clinician would have a different approach. I tell them the components and what the origins are of those components.

DR. PATTERS: Ray, I agree with almost everything that you just said, except you said that the P-15 has been shown to have some positive benefit. What was the data that supported that?

DR. YUKNA: I said might have.

DR. PATTERS: What is the data that supports that it might?

DR. YUKNA: The in vitro and in vivo information that I reviewed and, again, the clinical experience with the multicenter study seems to indicate some additional things are going on. At the very worst --

DR. PATTERS: I agree but what are they?

DR. YUKNA: Well, that the cells may be attracted more preferentially; that we seem to eventually end up with

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a nicer result. At the very least, there is almost no downside to it. In fact, there is absolutely no downside that I can see to this material and, given that it might be equal or have the potential to be better -- the same reason we used demineralized freeze-dried, it has the potential to be better than some of the other materials and that is not proven. If you look at our studies, as you know, there is nothing that shows up better than anything else so far.

DR. PATTERS: Thank you.

DR. TOFE: I think it may help the discussion if we read what we supplied to you all for the indications and uses so you can understand what we have in the labeling:

OsteoGraf/CS particles are intended to be used for the treatment of intrabony periodontal osseous defects due to moderate or severe periodontitis, period.

DR. REKOW: And the labeling is in this thing that is in your handout. So, do I hear a consensus that the "CS" in the name needs to be carefully taken care of by the clinicians but that there is nothing implicit in what the company is saying that suggests a claim, other than the fact that the clinical studies as they have shown them, in their estimation, provides an advantage to the patient? Is that a consensus?

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DR. GLOWACKI: No, I don't agree with that because I think the P-15 peptide is identified as a cell attachment peptide and, therefore, implicit in it is that it is a claim that there is an attachment effect by adding that into the product.

DR. REKOW: Okay. I am a little confused if we are talking about one or two.

DR. GLOWACKI: I am talking about one. CS, cell stimulating, is a device claim -- cell stickiness.

DR. TOFE: Excuse me again, our labeling does not say that. I understand where you are coming from, Dr. Glowacki, but there is nothing in the labeling related to this cell stimulation or the confusion around it or what is potentially claimed. In fact, if you look through the complete PMA document you don't see the words cell stimulation per se. I mean, it is not there; we don't use it. The labeling is: intended to be used for treatment of intrabony periodontal osseous defects due to moderate or severe periodontitis, period.

DR. GLOWACKI: If FDA wants to change that question, then we can consider a different question. I am talking about that question.

DR. REKOW: As it appears on the screen.

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MR. ULATOWSKI: Tim Ulatowski. It is important to recognize that labeling constitutes not only the package insert but also the label of the product, which may describe what is included in the product, and in terms of labels we have come across stated ingredients or acronyms or something of that sort that have a clinical inference or a meaning or importance that is not necessarily expanded upon or described in the labeling itself per se but that simply, by its statement, has an impact.

So, we ask the Panel in number one and number two whether that statement on the label by itself has impact and meaning to you as clinicians and scientists, and could be interpreted by any clinician out there or scientist to have some impact and meaning.

DR. REKOW: Yes, Floyd?

MR. LARSON: I think the thing that may be biasing this discussion is the fact that the words cell stimulating were used in describing the question and, according to the company, that is not the intent of CS. So, at some point it has been expressed that way so, obviously, somebody heard it that way but if it is very clear that it will not be used that way, I think that should be sufficient, if the company can assure us that it won't be used that way.

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DR. TENENBAUM: So, can I ask then what "CS" would stand for in the name? I mean, why is it there?

DR. TOFE: The name was Latin, cytostagin. It is just a name. I mean, if that is a hangup, change it.

DR. TENENBAUM: That is why I am asking. Having the "CS" designation, whether it means cell stickiness or cell silliness --

(Laughter)

-- to me suggests that this is the new and improved version of something, and has some biological activity.

DR. TOFE: It has probably gotten way out of proportion.

DR. AMAR: Would you be willing just to drop the CS-300?

DR. TOFE: The question to drop the CS-300, you have to have XY-300 or some identification otherwise the clinician would never know what the product is.

DR. AMAR: We will go with XY!

DR. REKOW: I will put a statement out and I am sure it will be shot down if other people on the Panel don't agree. I think it is clear that CS, in the minds of this Panel, is a problem that implies a claim and that some other

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designation needs to be used that has less probability of conjuring up a statement that says that it is the new, improved, active biologic material.

DR. GLOWACKI: My problem with that is that anything used to identify that the P-15 peptide is added to this constitutes a device claim because that P-15 is identified as a cell attachment peptide. So, even if you call it XY as an abbreviation for P-15, it still has that action of the added peptide as part of the device claim.

DR. REKOW: I think we have to be a little careful though because there is, you know, the Mercedes 300 and 400 and 500, and there needs to be some mechanism that industry can use to differentiate one product from another.

DR. GLOWACKI: Yes, that is fine but I would like to hear what the name is going to be.

DR. TOFE: Julie, one question, the description in the package insert, P-15 is a synthetic short chain peptide which mimics the cell binding domain of collagen. That is the quote. It doesn't make the cell binding statement claim.

DR. GLOWACKI: It does.

DR. TOFE: Well, I mean, a synthetic short chain peptide which mimics the cell binding domain of collagen.

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That is the extent of it.

DR. GLOWACKI: But that is the biological action, Dr. Tofe.

DR. TOFE: I appreciate that but the labeling requires us to put something down, but the clinicians want to know it is not just a matrix.

DR. GLOWACKI: That is why I think the answer to this question, whatever you replace that with, must be yes. The identification of this, because it contains a peptide with activity and not just a random sequence is a device claim because that component, even if it is not identified with a paragraph describing or giving reference to it, is that it is a cell binding peptide.

DR. TOFE: Should that mean then that we put P-15 on it or describe what is on it?

DR. GLOWACKI: It is the same thing.

DR. TOFE: That is the whole point, you have to put something down.

DR. GLOWACKI: It is a claim. I think all the discussion is, is this a claim? It is not an inert material that improves, but it is implying a mechanism that is increasing the cellularity around the implant material, and I think there is no way around that with regard to it being

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a device claim.

MR. ULATOWSKI: Just a point of order. It may seem bureaucratic but, first of all, this is a committee discussion, period, and the company provides their comment at the Chairperson's pleasure. They are not part of the discussion at this point. So, they must be recognized through you for further comment.

DR. REKOW: Okay.

MR. ULATOWSKI: The second part is, and I think Dr. Glowacki has already touched upon the point, that a product is what a product says it is and you have to address it in terms of all claims that are made for the product. I think now that we are starting to strip some things perhaps from the label, we have to watch out we don't get into a situation where we are back to a 510(k). I mean, if that is the case, fine, but we are going to lose the discrimination of the product here pretty soon if we start coughing up P-15 as well for the company and they are back to the "get-go" from three years ago. So, there is some middle ground here that is going to have to be reached if the company thinks this is going to be somewhere.

DR. REKOW: Okay. Well, is there anything else that we need to say as a Panel about question one? It seems

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clear to my mind that, whatever, it seems to have a claim and it is going to be part of a claim.

DR. GLOWACKI: Can we have a vote on that so we can see what the Panel views individually?

DR. REKOW: Okay. Does somebody want to state a hypothesis that we will agree or disagree with?

MR. LARSON: I guess seeing the direction in which it is going, I will make the comment that I was going to make before, and that is an analogy that you might consider which is HA coatings on orthopedic implants, I don't want to send the company back to the 510(k) process but there is a case where clinical work was done to present a PMA and one company decided to try a 510(k) and it was cleared. It was cleared as substantially equivalent to a device without HA coating on it. FDA, I think, has had a lot of problems with the question of implied claims in that area but at least there is an example of something like that that was cleared without any special claims. It may be that it is appropriate in this case, if you are concerned about the claims, to just say this PMA can be granted with some innocuous designation to it. You still can't call it "pixy dust" but you have to call it something. But I think the specific indications is where the focus has to be.

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DR. REKOW: Go ahead, Dr. Jordan.

DR. JORDAN: For me, it is hard to look at number one. One and two are intertwined. If N-300 is cell stimulating, then looking at this as another form of N-300 is no problem. It is another form of N-300. The problem I have comes when we add the P-15. If P-15 is supposed to make this different or better, without a study showing that it is different or better, I am trapped because I can't see how you can say that. You can make the claim that it is a cell stimulating product if N-300 is a cell stimulating product; it is just another one. Here is a Mercedes, here is a Cadillac. But if you are going to say that this Mercedes is faster because it has this added to it but you haven't compared it to the other, then it is very hard. So, the P-15 is the part that I am trapped with and it is hard to sort of go from number one without looking at number two. I have no problem with saying cell stimulating. It is another cell stimulating. Someone may say CS-500 tomorrow and it doesn't matter. That is not, to me, a real concern if, in fact, N-300 can also be a "CS" product. When it gets down to P-15, that is where, to me, the problem comes because we haven't gotten any validation that P-15 has caused anything.

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DR. REKOW: Well, let's take the first question as it is stated, does the name CS, cell stimulating, constitute a device claim? Let's go around and say yes or no to that question, and then we will go on to the second one. I will start with you, Dr. Janosky.

DR. JANOSKY: Wonderful! If I listen to the discussion here and I also recall a point that the sponsor had made that the product which started with the letter "N" actually stood for something that the clinician can tap onto and remember what the product means, I think in that same vein "CS" is going to be linked to something. So that name is going to recall something in a clinician's and maybe a patient's mind. So in that respect I think the answer is yes.

DR. TRUMMEL: I agree. My answer is yes.

DR. TENENBAUM: I agree that it constitutes a device claim.

DR. GLOWACKI: I agree. It constitutes a device claim.

DR. JORDAN: Yes.

MR. LARSON: I don't have a vote.

DR. REKOW: You can give your opinion if you choose.

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MR. LARSON: As it is worded there, yes.

DR. REKOW: Okay.

MR. LARSON: But I think the wording is incorrect.

DR. PATTERS: Yes.

DR. AMAR: Yes.

DR. STEPHENS: Yes.

DR. REKOW: Okay. We will now courageously proceed to number two, which says, does the stated presence of P-15 constitute a claim of clinical utility or clinical effectiveness for this device? Do we need more conversation about that?

(No response)

Okay, I will call the question, and we will start with Dr. Stephens this time.

DR. STEPHENS: I would say yes. I think one and two are almost identical. If P-15 is there, it has to be there for a reason and, either implied or real, it is going to be carried as a claim of clinical utility for the device.

DR. AMAR: I would tend to concur with the comment that, in fact, the presence of P-15 constitutes clinical utility vis-a-vis the periodontist or dentist.

DR. PATTERS: I am more concerned about the P-15, actually, because when they state in their description that

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it mimics the cell binding region of collagen I think that a clinician will interpret that to mean that it has some efficacy regarding cell binding, and I am concerned that they have not established that to my satisfaction. So, yes, I think it does.

DR. REKOW: Mr. Larson? You pass? Dr. Jordan?

DR. JORDAN: Yes.

DR. GLOWACKI: Yes.

DR. TENENBAUM: Yes.

DR. TRUMMEL: Yes.

DR. JANOSKY: Yes.

DR. REKOW: Do you, as the sponsor, want to respond to the first two? That seems to be one subset and the next one seems to be another subset.

DR. YUKNA: As far as number two is concerned, you know, the product, as tested, the CS-300 which had the P-15 on it did demonstrate clinical utility and clinical effectiveness. So, the presence of P-15 is included in that response, in my opinion and in my experience. Just remember that CS-300 is a unique device, shown in the clinical trial to have very good effectiveness. So, we feel that a device that does include P-15 in its components does have clinical utility and clinical effectiveness and that is how it works,

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or how it seems to work in providing the clinical differences that we saw.

DR. TOFE: We are very open to suggestions on how to use this word. I understand the concern. Clearly, answering yes to number two is obviously that there is some type of a clinical impact. The question we are struggling with is finding how we "define" this OsteoGraf-blank.

DR. REKOW: Is it the purview of this Panel to do that? Are we, as a Panel, supposed to provide this leadership or is that conversation that takes place between you and the sponsor later?

MR. ULATOWSKI: Now that you have answered question one and two, it sets up the following questions. You could have answered one and two no and then continued to answer the follow-up questions in a little different way. Given the intended use statement and the implication of P-15 and "CS" as you have voted upon in answering the questions, now you can approach study design and additional data, labeling recommendations to address these issues.

DR. REKOW: Let's go through the questions then and then come back to the directions and choices that we have available to us.

The next one is, is the study design appropriate

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to establish safety and effectiveness as labeled? Let me read it from the text here. It says, is the fundamental study design appropriate to establish the safety and effectiveness of CS-300 as labeled, including all claims, i.e., cell stimulation, restoration of lost bone, etc.? Is the fundamental study design appropriate?

We have had some discussion about that. Shall we have some more or are you ready to voice your opinion, Dr. Patters?

DR. PATTERS: Well, the way that question is worded, certainly I think we have covered the cell stimulation issue.

DR. REKOW: Yes.

DR. PATTERS: On the other hand, I know there are some statistical concerns about the "n" and I have also been out there trying to recruit patients for such studies, and I am extremely sympathetic and I admire their accomplishments. To me, this is one of the best trials in my five or six years of being on and off this Panel that has been presented. I think it is an excellent trial. Clearly, I have no question that the trial has demonstrated safety and efficacy of the device.

There is a Catch-22, however, because of questions

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one and two that we are going to come back to. But I agree, as Dr. Tenenbaum pointed out earlier, that it is an excellent trial and I think the company should be commended for their efforts. Thirty-one doesn't sound like a lot of patients. You try it and you will see!

(Laughter)

DR. AMAR: I vocalized the credit earlier and I definitely commend the sponsor for this study. The only problem is the last part of the question which is related "as labeled." That could be addressed in many, many ways. Definitely the study design is appropriate to establish safety and somehow efficacy.

DR. REKOW: Dr. Tenenbaum, did you have something you wanted to say?

DR. TENENBAUM: Yes, it may sound like a bizarre suggestion but Dr. Patters raised an idea of post-approval studies --

DR. AMAR: Surveillance.

-- postmarketing studies. Then I tried to tie that in with the labeling. Would it be completely bizarre to include something in the label saying that at this time OsteoGraf/CS-whatever with P-15 has not been demonstrated to be more effective than OsteoGraf/N? If that was on the

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label and then postmarket studies were done, is that appropriate? It is sort of like the Surgeon General's warning. I don't know.

DR. REKOW: Go ahead, Tim.

MR. ULATOWSKI: Well, there are any number of ways you can approach it in terms of postmarket studies and labeling. Labeling, as you know, is to describe what you got and, in as much as labeling might describe that the clinical evidence has not been shown to prove its cell stickiness, stimulating or whatever, you would say that in labeling and then proceed on a post-rule study in order to support such labeling. So, you know, we are at the pleasure of the Panel to see what you may come up with here.

DR. TENENBAUM: Further to that issue, I can't say enough on how well done I thought the study was. So, we do have, as I say, a Catch-22 -- or as I whispered to somebody, a Catch-15 --

(Laughter)

-- but I still feel that this is an important issue and, yet, I agree that your study has answered some of the questions but there is still the nagging question of why do you have the P-15 in there. If I am treating a patient I have to tell him there is P-15 in there, and why is it

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there? So I, as a clinician, would be very happy -- taking off my scientist's hat -- to say to a patient, "well, this has not been shown to be better yet than the regular OsteoGraf; those studies are being done. But it is certainly safe and effective in the milieu in which it was originally tested.

DR. REKOW: Why don't we take a ten-minute physiologic break while we consider in our own minds what safety and efficacy has been shown by the studies that we, as a Panel, would be comfortable with, and then we can go on to where else we could go: what labeling concerns we have; what sorts of other issues need to be taken into account. But let's find out how far we can go that we are comfortable with and, you know, what is the upper limit of what claims can be made and what could be put on the label, and then go on from there to see what else it would take to make any changes beyond that. Is that a reasonable approach to all of this? How about ten minutes?

(Brief recess)

DR. REKOW: I think that where we got to was that we can go some place but we are not sure we can go all the way with this process. So, we have two alternatives. We can continue going through the questions as they appear, or

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we could get a motion from the floor about what upper limit we thing we can go to and then make recommendations on how we can proceed beyond that. What is the pleasure of the group? Yes, Dr. Trummel?

DR. TRUMMEL: I will defer.

MR. ULATOWSKI: Well, the FDA would prefer that you proceed through the questions. I think the questions, maybe not as directly as you would like, get at the issues at hand. For example, you have answered questions one and two.

DR. REKOW: Okay.

MR. ULATOWSKI: Number three -- let me just say hypothetically in answer to number three, number three, you could say, well, the study design is not appropriate for whatever reasons. It is not as appropriate as we would like for the following reasons, and the following improvements could have been made, and then later on say that these matters could be addressed in a post-approval study, or they could be addressed in another pre-approval study. So you could follow that kind of train of thought.

DR. REKOW: Okay, you have heard the charge. So, the third question is, is the fundamental study design appropriate to establish the safety and effectiveness of

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CS-300 as labeled, including all claims? Dr. Trummel?

DR. TRUMMEL: I am comfortable with the safety of the product. I am not comfortable with the demonstration of establishment of effectiveness as labeled. I believe it is strongly implied in the labeling that P-15 is an active component of this material, and I do not believe the study design has established that it is active, or more active as the combination than the single agent alone. So I would vote no as this question is articulated.

DR. REKOW: Mark?

DR. PATTERS: I think we are right back to the heart of the difficult issue again. Clearly, if there was no P-15, if this was some type of new product, I feel, and I speak only for myself, that you have demonstrated safety and efficacy in your clinical trial. The issue here comes down to the fact that you have placed this P-15 on it. You feel it has some important physiological benefit, which you have hinted at and it was in in vitro studies but have no direct in vivo data, and I think the only solution to this is that you are going to have to get that data and everybody is going to be happy. I see no way around this.

I don't see how we can have partial labeling in any way that says that there is P-15 in here and the

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clinician says, "okay, what's that? What does it do?"  
Because we can't answer the question. I know you have  
worked hard on this and I know it has been costly and you  
have done a tremendous job but, unfortunately, it is just  
not finished. It is going to take another six months or  
more to finish it.

DR. STEPHENS: I agree. I think that is really  
the heart of the issue. I think this is the first of these  
new products with a bone filler with a component that is  
added to stimulate bone formation, and I think that we need  
to know whether or not it is, in fact, doing that and  
whether or not both these components are working to  
stimulate bone formation. I think then what we have is a  
CS-300 that works in spite of the fact that the P-15 is on  
it, and I think we really need to know whether it works;  
what the two components are doing.

DR. REKOW: Any other comments from the Panel?

(No response)

So, if we take this question as it currently is  
stated, and go around, is the answer yes or no? Is the  
study appropriate to establish the safety and effectiveness?

DR. PATTERS: Excuse me, the statement up on the  
slide there and the statement in here are not the same. I

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cannot answer them the same so I need to know which one you are talking about.

DR. REKOW: The one that is written, that says is the fundamental study design appropriate to establish the safety and effectiveness of CS-300 as labeled, including all claims, i.e., cell stimulation, restoration of lost bone, etc.?

DR. PATTERS: Well, if I was the sponsor I would be somewhat concerned because they are not making those claims.

DR. TOFE: We are not making that claim and I keep going back to this. I keep going back to it and I keep reading it. We are not making this claim of cell stimulation. I don't know why that keeps resurfacing.

DR. REKOW: Tim?

MR. ULATOWSKI: I think we have come to terms on what "CS" means. I don't want to hinge it on stimulating or whatever, but I think you have answered number one and two as yes, which says that the Panel has already agreed that "CS" and P-15 contribute a clinical impact to the use of the product. The question states "as labeled" and by that we meant all labeling, the P-15, "CS", the intended use statement.

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DR. REKOW: Yes, Floyd?

MR. LARSON: I think it would be only fair to accept both what we have in writing in the indications for use and statements of the sponsor regarding, if not past intentions, at least present intentions and their assurance to us regarding the use of the term cell stimulating, and strike that from the question before it is voted on. Would it be appropriate to amend the question based on the sponsor's current representations to us?

DR. REKOW: Go ahead, Dr. Amar.

DR. AMAR: When I read the recommendation in question number three, it comes to my mind that one of the claims is definitely restoration of lost bone. If we come back to that as being the target of what we are discussing, somehow this material demonstrates restoration of bone loss. Whether it is P-15 or not, that is a different issue. But, if the sponsor agrees, I would stick on the restoration of lost bone.

DR. REKOW: Again, I will take the Chairman's prerogative. I think we have danced around this question as it currently stands and I would like to propose that we address the question is the fundamental study design appropriate to establish the safety and effectiveness of

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CS-300 for the restoration of lost bone.

DR. GLOWACKI: As labeled.

DR. REKOW: All right, as labeled. Whether or not we keep the "CS". We have already had that discussion. Let's not get hung up on that part of it again. Can we address it without the "CS" first and just for the restoration of lost bone? Yes, Tim?

MR. ULATOWSKI: Yes, you could, in order to get some progress here. But keep in mind that there is an existing claim here for P-15. So, you have to follow with number three in the full context and substance of the labeling claims for the product. We are talking about study design here. The background was if you have a P-15 claim with a collagen-like claim, then did you need another arm to the study? Would that have been appropriate? So we are looking at design issues specifically, not within the totality of the study, for number three.

DR. AMAR: If the claim is no longer cell stimulation or cell sticking, it falls into the bag of restoration of bone loss, then the arm of the positive control, which is demineralized freeze-dried graft, is appropriate to me.

MR. ULATOWSKI: Then what do you make of the P-15?

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DR. AMAR: Oh, that is a different story. It could be a composition of ingredients without any claim -- calcium phosphate contains calcium, contains phosphate. It contains P-15. If the claim is no longer cell stimulation or cell sticking or anything related to that, because I understand that the Panel has some serious concern about that -- if the claim is back to restoration of bone loss and it is well disclosed that it contains calcium phosphate and some peptide amino acids in a sequence, why not?

DR. REKOW: Yes, Clarence?

DR. TRUMMEL: Dr. Patters pointed out earlier that in the description of the product it says and P-15 is a synthetic short chain peptide which mimics the cell binding region of collagen. To me, that word "mimics" suggests a biological property of this material. Yes, it appears to result in bone regeneration but is it because of the addition of the P-15? I cannot tell from the study design.

DR. AMAR: Just a comment, obviously the labeling has to be changed.

DR. REKOW: Floyd has a comment.

MR. LARSON: I just wanted to ask the Chairman if she would ask the sponsor whether they would be willing to give up that part of the description if approval hinged on

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it.

DR. REKOW: I will ask the question.

DR. TOFE: We would obviously, but for Dr. Trummel, maybe the word analog may be a little more -- or whatever. That is not an issue with us. Again, I understand the concern but I don't know what the right words are.

DR. REKOW: Tim?

MR. ULATOWSKI: If I might suggest, there is labeling as stated, and you have made a decision on one and two. You can flow through the questions. The last question really is, okay, given the state of affairs and the way it is, how can we mitigate the situation through labeling, through pre and post-approval studies, whatever? So, our logic was to flow through it as the package stands and then to let the Panel recommend changes or factors to mitigate the situation.

DR. REKOW: So, as the question stands -- is there anyone who would object to saying that the answer to number three, as the question currently stands, is no?

DR. PATTERS: Well, if you took off "as labeled" I would say it is yes, but with "as labeled" on I would say no.

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DR. REKOW: Okay, but I am hearing the FDA saying we need to do it as it currently states. So, as labeled the answer is no. The next one please.

MR. LARSON: I am sorry, I do have a problem with that because at this point cell stimulation is not a claim. Maybe it has been in the past but it is not now.

MR. ULATOWSKI: At the end, as I said, we will come to those mitigating factors --

MR. LARSON: Okay.

MR. ULATOWSKI: -- to the company. Now that you have heard the story, what do you propose to do, and how does that then change our recommendations to items three, four and five?

MR. LARSON: The answer to question three seems so final.

MR. ULATOWSKI: No -- well, it is final; it is based upon the package as it stands.

DR. REKOW: So, again, our charge is to do the package as it stands and then we will negotiate. Number four as it stands, are the indications and claims for this device supported by sufficient data to demonstrate the safety and efficacy of the device? That does seem an awful lot like number three.

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MR. LARSON: No, that is a different question.

DR. REKOW: It is different but it is hard to have one without the other, isn't it? Any discussion on number four?

(No response)

Is there an answer other than no with all of the caveats that we have at the moment?

MR. LARSON: Again, I have a problem with the use of the word "claims" with a misinterpretation of the current claims. You know, are the indications and stated claims by the sponsor supported by sufficient data? I think the answer is yes.

DR. REKOW: Okay.

DR. AMAR: I ask the Chair to ask the sponsor whether the sponsor would restate the claims of this material.

DR. REKOW: I think I would like to put that question off till the end and follow FDA's request that we go through all six questions and then come back.

DR. AMAR: I mean, I am coming to this situation, if the claims are misinterpreted, let's have it right.

MR. LARSON: Or even if they have been changed.

MR. ULATOWSKI: I would suggest we keep that

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conclusion for the last question here.

DR. REKOW: Excuse me?

MR. ULATOWSKI: To keep that point as the last question here and then cycle back through again, cycle back through with any changes or modifications.

DR. REKOW: Okay. So, we will move right on then to question five, which is, does the Panel feel that the study sample size is sufficient to represent the patient population into which this device is to be implanted?

I think this is a little bit different than some of the others and perhaps it warrants some conversation, some discussion about that. Is there a need for more?

(No response)

Okay, I will ask the question. This time we will start with you, Dr. Jordan. Does the Panel feel that the study sample size is sufficient to represent the patient population into which the device is to be implanted?

DR. JORDAN: Yes.

DR. REKOW: Dr. Glowacki?

DR. GLOWACKI: I have heard a number of concerns about the generalizability of the conclusions that were drawn from the study as designed, and would say no.

DR. TENENBAUM: I think that as it stands the

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sample size was adequate for the question, ignoring the P-15 element.

DR. REKOW: Okay. Dr. Trummel?

DR. TRUMMEL: As far as safety, yes. I am a little less comfortable with efficacy but I would have to come down on the side of yes for efficacy as well.

DR. REKOW: Dr. Janosky?

DR. JANOSKY: No.

DR. REKOW: Mr. Larson, would you like to answer this one or would you choose not to?

MR. LARSON: I would say yes.

DR. PATTERS: Yes, the sample size is sufficient.

DR. AMAR: Yes, the sample size is sufficient based on what we see in the periodontal literature, as pointed out this morning, where 15 patients are sufficient to warrant the power and, in fact, it is true, there is sufficient power for the analysis.

DR. STEPHENS: I would say yes. I think that the FDA was involved in this from the beginning so I don't see any problem.

DR. REKOW: So we have an answer that seems to be coming down on the side of yes but not as conclusively as I suspect some members in the room would like it to be.

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Then we will go on to number six, which really gives us room for negotiation, which says does the Panel have other recommendations to address outstanding issues or concerns, for instance, labeling recommendations, pre and post-approval studies, modification of device claims.

As a clarification for me, Tim, you would like us to address those before we take the vote?

MR. ULATOWSKI: Yes, because it sets up the vote.

DR. REKOW: Okay. So, Dr. Tenenbaum?

DR. TENENBAUM: As I alluded to earlier, labeling I think is extremely important for this type product, and given all the issues that we discussed, at the very least at this moment if it was appropriate to include information in the label -- OsteoGraf/CS-300 has not been demonstrated to be superior to OsteoGraf/N or other HA materials -- then I think that tells exactly what we have at this moment.

Then if I can talk further about recommendations, which I think is what we are looking at, then as part of the whole picture the recommendation is, strong recommendation, that the actual comparison be done, I mean at the very least, between the CS-300 and the hydroxyapatite. I can't see any other way around it. If that can't be done, if that issue is not addressed then I don't see any way around it

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but having to go back to the drawing board.

DR. PATTERS: Well, I would like to go back to my earlier point. They have to disclose what is in the product, and what is in the product is natural hydroxyapatite and a 15-amino acid chain peptide. They have to disclose that on the labeling.

Then the next question is, all right, we know a lot about hydroxyapatite, what is this straight chain peptide for? Well, they have to say something as to why it is in the product, and I am not sure there is labeling which would satisfy the Panel to describe why this is in the product without actually conducting the studies. That is my concern.

DR. REKOW: The studies being?

DR. PATTERS: To compare the P-15 natural hydroxyapatite product with the plain N-300 hydroxyapatite to show the clinical benefit of P-15 in an absolute sense. I just don't know how they can label the product and describe what is in it without implying a claim. Just the description implies the claim that this comes from collagen. It comes from a certain region of collagen known to participate in an important physiological function. So just the description of it implies a claim. So I just don't see

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any way out for them. I think it is unfortunate. They have conducted a very good study. They appear to have a very good product. It could be the first generation of a very important approach to restoration of bone. I would like to see the product on the market personally. On the other hand, I think we need to have the questions answered and I don't think that there is, in my mind, a compromise available to describe what is in this product without making a claim that at this point is not substantiated. That is how I see it.

DR. REKOW: Any other discussion? Would someone like to make this as a recommendation that we can have as a motion to deal with?

DR. TENENBAUM: Can I make one other comment? Again, I still have to really reconcile these issues in my mind but, again, to echo a bit of what Dr. Patters said, even if it ultimately comes down that the committee decides that we can't somehow reconcile these problems, this study certainly is not a wasted study. This is part of the whole information package that is ultimately needed anyway. This is a well done study. It provides an important body of data. So, it is not as if this study is not important or not as if that study will not play a role one way or the

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other. My suggestions are being made to try to see if we can take a step forward instead of two back, I guess -- the original suggestion I made.

DR. REKOW: Yes, please?

DR. TOFE: Can I make a comment? From CeraMed Dental, as far as the labeling, I am sure in negotiation with the FDA we can work out something which will get away from this concern.

Also, clearly we have no problem addressing this scientific question of the "N" versus the "CS" in a well designed study as a post-approval process. We understand that and we hear your concern loud and clear, but we would like to be able to do that on a post-approval status.

DR. REKOW: Is anyone on the Panel willing to make a formal statement of the recommendation, or are you going to force me to do this?

Let's bring up the question of the pre or post-approval. Let me backtrack a little bit. It seems clear that there is a need to show the clinical benefit of P-15 through comparison between the 300 material with and without the P-15. Is that an accurate statement?

Then the next part of it comes to should that be done before the approval is given, or is it reasonable to do

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it as a postmarket approval consideration? I would like the thoughts of the Panel on that.

DR. AMAR: And what would be on the label if it is on a postmarket surveillance basis?

DR. TENENBAUM: Well, the only way that I could support in any way this being approved and then postmarket studies being done would be if the label was changed to take out even the collagen binding activity, just to say that there is a 15-amino acid peptide that is being added and that, further, there is no evidence that this product is superior to OsteoGraf/N or other HA-containing products. I understand that even that is very uncomfortable for some members of the Panel, including myself to be honest with you, but that is the only way I can see possibly approving this and then going for the postmarket study, which we all agree I think is the same study, that is, HA plus P-15 versus HA.

DR. AMAR: Well, as I stated earlier, could the sponsor just restate the claims?

DR. TOFE: I think that could be done with the labeling with FDA negotiations. To answer the question, yes.

DR. REKOW: Would someone like to be bold and make

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a proposal that we could consider? Dr. Jordan, you were going to say something.

DR. JORDAN: Yes, but I don't know what. There is something still missing. What are the consequences of pre or post labeling? My concern is I feel like we are now approving another OsteoGraf/N product that is going to be then marketed to see if, in fact, it is better than the other OsteoGraf/N product, and I am having a hard time figuring out why that wasn't done beforehand. Why are we here now, doing this with all the intelligence we have here, when this is sticking out so obviously? How did we miss this? It is not like it is a subtle thing that has been found, but it is a very obvious thing and it is very hard to understand how something being so obvious has been missed until we got to this point.

And pre-approving or post-approving has very grave consequences. To post-approve something, if you then study it and you find there is no efficacy or, in fact, it is not even as good as OsteoGraf/N, what have we done? Why wasn't it done beforehand? I mean, this is not something that is a needle in a haystack. How did we miss it and get to this point without studying it beforehand? Even in five patients? With the small number of patients that it takes

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to do this, then I raise the question why couldn't that have been five patients studied to at least give an idea? Two patients? But, certainly, I have a hard time understanding how we have gotten to this point and I feel uncomfortable with that because I think we have the potential of making a decision that has some very big consequences, and I want to have the FDA sort of come on where they are because I am not sure, just sitting here, that is what I want to do. I have a hard time believing this wasn't discussed before now.

DR. PATTERS: For those who read the PMA, there are a number of letters between the sponsor and FDA where FDA says we would also like you to compare this with the N-300. They were asked to do that a number of times and they responded in different ways, essentially saying that they could not test that in the present protocol. And I understand that but, of course, they were not limited to one study. They could have done multiple studies. So, it is not a new concern that is raised here. It was raised by FDA several times.

DR. YUKNA: But in the scheme of things and discussing and developing the protocol with the FDA this did come up, and the protocol, as it was enacted, was with the approval of the FDA to utilize the predominant treatments of

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DFDBA and debridement and not include the OsteoGraf/N.

I agree that a number of different additional studies could be done, and given the questions here, hopefully in postmarket approval status they will be done. But this was an arbitrary decision on my part in developing the protocol, or the company's part, the sponsor's part in supporting that protocol. That protocol was developed and discussed on several occasions with the people here at the FDA.

DR. REKOW: Tim?

MR. ULATOWSKI: Just a couple of points. At the beginning of an investigational study FDA will consider the protocol as submitted and evaluate the safety of the product for initial human implantation or use, whatever the case may be. We will note potential issues that may come to bear at premarket approval time. But the onus is on the sponsor to move forward providing the product is fundamentally safe and there are no overt concerns to proceed. But you sink or swim, come to the panel time and the final decision.

I think the Panel is kind of walking the fence here a little bit. If you do an approval with a post-approval study, you have to be fundamentally comfortable that the device is safe and effective as

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labeled. Now, what is "as labeled?" Well, you have to make some recommendations on exactly what you are comfortable saying about this product or what the data show. You can't defer some of your fundamental efficacy concerns for the post-approval. The post-approval is intended to evaluate additional subjects, for example, to decrease concerns about the generalizability of the data, or long-term safety or efficacy, something like that. You are approving it for the product as labeled. If there is any hint, any direct or indirect statement regarding cell stickiness, collagen-like activity, whatever, that is what you are voting on for approval.

DR. REKOW: Thank you. Go ahead, Mark.

DR. PATTERS: I am concerned. Obviously the sponsor would like approval and the sponsor is willing to discuss labeling with FDA. But sitting here as a Panel member, I have trouble voting for approval without knowing what the labeling is likely to be and that they are going to agree upon. In my mind, the whole issue now has boiled down to labeling. How will it be labeled so that we can be comfortable that the product is, indeed, safe and efficacious as labeled. So, without knowing what the labeling is, I am having trouble recommending approval and

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then leaving it up to you guys to negotiate the label.

I was looking at this document as to all the things we could do, and one of the things FDA doesn't want us to do is table. I move to table until we see what the labeling will be.

MS. SCOTT: Maybe to help clarify your concern, Dr. Patters, the Panel can recommend labeling issues. One of the options is to vote that the PMA could be -- and I will go through all this before the actual motion, before the actual vote. But if the Panel feels that there are certain labeling changes or recommendations that they would like to make, that could be a part of a condition of approval.

DR. PATTERS: I understand that but I am concerned that there is no labeling at this point without conducting the studies that would satisfy myself or other members of the Panel. So, without knowing what that is likely to be, I am concerned.

DR. TENENBAUM: Just looking at question number six, labeling recommendations, I think at the very least, on the basis of the data we have now we could make labeling recommendations. That is, that the reference to the collagen cell binding region be removed and that, as I had

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said earlier, there is no demonstrated superiority of OsteoGraf/CS-300 to OsteoGraf/N or any other HA material. That is a recommendation that I think I could make for the labeling.

DR. AMAR: I was making the recommendation earlier and I was asking whether the Panel would agree on the labeling such as restoration of lost bone. I mean, it is clear, from the data that at least that part regarding bone fill, that this material acts in regeneration of lost bone.

DR. REKOW: Let me make a proposal. It seems to me that there are three functional things that we could do, that I have been hearing. One is to not approve this until the efficacy of P-15 relative to the "N" material has been shown. Another would be to approve it with some changes in labeling to be determined today and show the efficacy of P-15 in postmarket studies. The third would be to table it until we figure out what the labeling changes are going to be. We need to decide which of those three prongs we want to at least take a vote on.

MR. LARSON: The second.

DR. REKOW: So I hear a proposal. Do you want to make it as a motion?

MR. LARSON: I don't know, can a non-voting member

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make a motion?

DR. REKOW: Will one of the voting members choose one of those options so we can at least have a motion on the table and get to a Robert's Rules sort of thing? In the meantime, I am going to have Pam read what our choices are while you are making those considerations. The choices, again, are that nothing can be approved until the difference between P-15 and "N" is shown. The other is to change the labeling and do P-15 after the fact. A third one is to table it until we figure out what the changes in labeling are.

MS. SCOTT: Panel recommendation options for premarket approval applications. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence, that the

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probable benefits to health under conditions of use outweigh any probably risk. Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows. Approval with no conditions attached. The Agency action would be as follows. If the Agency agrees with the panel recommendation an approval letter will be sent to the applicant.

Second, approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting, all of the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's response to the conditions of your approval recommendation you want, for example, FDA or panel. Panel follow-up is usually done through homework assignments to the primary reviewers of the application, or to other specified members of the panel. A formal discussion of the application at a

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future panel meeting is not usually held.

If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points: a) the purpose of the requirement; b) the number of subjects to be evaluated; and, c) the reports that should be required to be submitted.

The Agency action. If the FDA agrees with the panel recommendation an approvable with conditions letter will be sent.

The third choice, not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations: a) the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; b) reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling; and, c) based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that

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you identify the measures that you think are necessary for the application to be placed in an approvable form.

Agency action. If FDA agrees with the panel's not approvable recommendation, we will send a not approvable letter. This is not a final Agency action on the PMA. The applicant has the opportunity to amend the PMA to supply the requested information. The amended application will be reviewed by the panel at a future meeting unless the panel requests otherwise.

Fourth, tabling. In rare circumstances the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant, thereby, creating ambiguity and delay in the process. Therefore, we discourage tabling of an application. The panel should consider a non-approvable or approvable with conditions recommendation that gives clearly described corrective steps. If the panel does not vote to table a PMA the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the vote the chairman will ask each panel member to present a brief statement outlining the reasons for their vote.

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DR. JORDAN: I have a question.

DR. REKOW: Yes?

DR. JORDAN: Based on what you just read, is it possible to vote to approve this pending an X number of patients studied comparing OsteoGraf/CS with OsteoGraf/N, and based on that data the labeling will either attest to this product's superiority, parity or inferiority to OsteoGraf/N.

DR. REKOW: That sounds like it is approval with conditions.

DR. JORDAN: I have no problem to approve this if they do a study. If they do a 5-patient study and they show that OsteoGraf/N is better than this, then the labeling should say so. If they do a 5-patient study and they show this is better than that the labeling should show that. But if it showed that they are both the same, then the labeling should show that also. I have no problem in voting to approve this but I think I want to have that condition. I think that is the concern that most of us have.

DR. REKOW: That is possible to do, approval with conditions and you, as a Panel, can set the conditions.

DR. AMAR: Would they market the product in the meantime, while they are doing the studies?

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MS. SCOTT: Yes.

DR. STEPHENS: If it is approvable with conditions?

MS. SCOTT: Yes.

DR. AMAR: Then again the question is what would be the label.

MR. ULATOWSKI: Well, the approvable typically means ultimately an approval with a postmarket study, but it could also mean some items to tidy up before approval, before it even hits the market.

DR. AMAR: Well, that is an option then.

MR. ULATOWSKI: Yes.

DR. REKOW: So do I hear a proposal from anyone?

DR. JORDAN: Just a question, how long does it take to do this kind of study if you are going to do five patients?

DR. YUKNA: Well, first of all, would 5 be enough to satisfy the concerns you have when 31 wasn't enough for the study? Really, 5 would not give you the information you need. It really wouldn't. I go back to the "n" of 22 because the clinical parameters would be the same, a minimum "n" of 22.

DR. JORDAN: How long would it take to do 22?

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DR. YUKNA: If you accept 6-month data with radiographs as major surrogate documentation, 6-month studies take at least a year to do.

DR. GLOWACKI: From what I heard from Miss Scott, if we vote for approvable it is the responsibility of this committee to sit here today and define what further information is required. For my part, I feel that it is not a question of small items and tidying up and looking for resorption rates or very specific information, and it would seem to me that the more appropriate thing would be for the sponsor to design the study, to work with the FDA to ensure that this committee and the FDA would all feel comfortable with the validity of the data that would be generated from that.

DR. REKOW: Would you like to formulate that into a recommendation, please?

DR. GLOWACKI: Okay. The recommendation would be for not approval on the basis of inadequate -- let me get those words right -- in the absence of reasonable assurances of effectiveness of the product which, I feel, must imply what the composition is, its effectiveness in a significant portion of the population.

MR. LARSON: A question.

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DR. REKOW: Yes?

MR. LARSON: I wonder if we can have Pam Scott read again the actual wording of that section because I heard something about under the conditions of use --

DR. REKOW: You have a copy too in your handout.

MR. LARSON: Excuse me.

DR. REKOW: That is okay.

DR. GLOWACKI: What I am saying then is items a), b) and c) would be the domain of this Panel with conditional approval, and I feel that is inadequate given the amount of information that we have already.

MR. LARSON: I think the focus needs to be on is it effective under the conditions of use prescribed, recommended or suggested in the labeling. I realize the hangup is the word "suggested" there and just the existence of the P-15. However, we still have to recognize that the material has been shown to be effective in restoring bone.

DR. GLOWACKI: I think my problem is that there have been many opportunities for the sponsor to give us hints at what the labeling would be and I haven't heard them, and I don't think that this Panel is able to generate them in sufficient time to vote for approval. So, that is why I am making my motion.

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MR. LARSON: Dr. Tenenbaum has made some specific recommendations that we could choose to act on as well. We could also ask the sponsor whether they are willing to accept those recommendations. I recognize that the sponsor has said they would work it out with FDA, but I think we are to the point where the sponsor is going to have to say something to this Panel about it. But, you know, are those recommendations sufficient to allow approval and would the sponsor agree to them?

DR. REKOW: Howard, would you restate your proposal?

DR. TENENBAUM: Is this a motion or a proposal that we find out whether the sponsor is willing to accept?

DR. GLOWACKI: Glowacki is willing to withdraw her motion so that Dr. Tenenbaum can make one.

DR. REKOW: Let's make it as a formal recommendation.

DR. TENENBAUM: I would recommend that the product be classified as approvable pending changes in the labeling, specifically indicating that OsteoGraf/CS-300 has not been demonstrated to have superiority to OsteoGraf/N or other HA implant materials and, further, that reference to the 15-peptide agent, P-15, be changed so that it does not refer

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to cell binding activity in any way, and that there be postmarket studies which are designed to demonstrate whether or not the addition of P-15 confers superiority of OsteoGraf/CS-300 over OsteoGraf/N or any other HA-containing implant material.

DR. JORDAN: Is that a motion?

DR. TENENBAUM: Yes, sir.

DR. JORDAN: I second it.

DR. REKOW: Okay, we have a motion and we have a second. The first question I am going to ask the corporate people is, is that an acceptable alternative from your perspective?

DR. TOFE: Yes, it is. From our perspective, yes, it is.

DR. REKOW: Oh, I am sorry, Dr. Jordan apparently isn't a voting member so can I have somebody who is a voting member second?

DR. TRUMMEL: I will second.

DR. REKOW: Okay, Dr. Trummel seconds it. Thank you.

DR. PATTERS: I have a question for Dr. Tenenbaum. How would you have the sponsor describe the P-15 in the labeling?

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DR. TENENBAUM: I think that is an excellent question --

(Laughter)

-- well, it is an important question.

DR. PATTERS: Can you think of labeling it some way that won't imply what it does?

DR. TENENBAUM: You have stumped me. All I can think of is that we indicate that this contains this peptide, or that the label indicates that this is a bone implant material containing calcium phosphate hydroxyapatite analog and a 15-amino acid peptide.

DR. PATTERS: So, I am the clinician reading this and I want to know what that is in there for, so I call up these people on the phone and say, "can you explain to me why you put this synthetic peptide in here," and what would you have them say?

DR. TENENBAUM: I would have to think about that.

DR. PATTERS: I mean, this has been my concern all along, that there may be no labeling that does not imply some utility. That is my concern.

DR. STEPHENS: But aren't we going to state in the label that the performance of it has not been established? Isn't that part of the labeling?

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DR. TENENBAUM: That is part of the labeling but the question, and I think a very valid question is the consumer, periodontist, whatever, wanting to know then what this P-15 is. At this moment, I don't have an answer to that but I think that these questions could be answered. Further, if there was no demonstrated superiority of P-15 with the appropriate studies, the approval would have to be withdrawn.

DR. PATTERS: A second question then. Do you mind if I address the sponsor, Madam Chair?

DR. REKOW: That is fine.

DR. PATTERS: I want to be sure that I understood correctly. Dr. Tenenbaum's proposal is that you label the product and that the product has not been shown to be superior to N-300 and you agree to do that?

DR. TOFE: Yes, I thought it was that it had not been tested against N-300 but, basically, yes, we are agreeable to that. But from a legal standpoint, all you really have to say is that P-15, a synthetic peptide, is in the ingredients, and that is the only place I believe in the labeling we are required to do that.

DR. PATTERS: You don't have to say why it is there or what it does?

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DR. TOFE: No, just as part of the ingredients.

DR. REKOW: Tim?

MR. ULATOWSKI: To modify, I think if you said P-15 you would have to say something about that ingredient in the labeling.

DR. PATTERS: How much?

MR. LARSON: As it is on the label, which is P-15, a synthetic peptide, period?

MR. ULATOWSKI: Well, I will tell you, I think you are between a rock and a hard place here.

DR. PATTERS: That is my point.

DR. AMAR: In general do they have to say anything about calcium phosphate present in hydroxyapatite?

MR. ULATOWSKI: Well, you should state the ingredients in the product.

DR. AMAR: Well, it could be a sequence of an amino acid.

DR. TENENBAUM: So they neutralize the claim somehow?

DR. AMAR: No, I am trying to escape from the rock and the hard place --

DR. TENENBAUM: I think the point is well taken. Calcium, for example, is a second messenger. It is a cell

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signaling agent, and so on, and do we have to talk about that?

DR. AMAR: Signalling? I don't know about that.

DR. TENENBAUM: Well, I am basically agreeing somewhat with what you are saying -- why do we have to explain what P-15 is, basically, if we don't have to explain what calcium does and what phosphate does. But I think Dr. Patters' question is still a very important question which I am not sure how to answer.

DR. AMAR: That is the reason I was making the suggestion to the Panel to call it just bone restorative material.

DR. REKOW: Dr. Glowacki, did you have something that you wanted to add?

DR. GLOWACKI: No.

DR. REKOW: Tim?

MR. ULATOWSKI: Well, back to a former point, if you start stripping claims and whatever you are going to end up with a 510(k) product again with no discrimination between that and N-300, because we could end up with a situation where claims are so emasculated that they are, you know, of no value.

DR. REKOW: Yes?

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DR. AMAR: No, the reason I have tried to emasculate the claims, if I may just quote you -- and we are not here to emasculate anybody -- is just to allow the sponsor, upon the suggestion of Dr. Tenenbaum, to put it in the market and give it some time for further studies. That is not to emasculate because that is a radical operation, I would say. This is just a transitional approach with a form of labeling that would be agreeable to this Panel, and leaving some time for the sponsor to conduct the studies.

MR. ULATOWSKI: Well, I would be more understanding, I guess, in evaluating the outcome of this if the Panel was of a bent that, given the in vitro and in vivo data and the current clinical data there was the evidence and the trend that there was an activity here. What I am trying to get at is that you have to have a fundamental comfort that there is something going on here with the P-15 to move forward, and then we can supplement that data but, you know, you have to cross that bridge.

DR. GLOWACKI: I think that is a perfect opportunity for me to remind the committee of my very careful evaluation of the preclinical studies came to the conclusion that the information that was warranted from those studies really doesn't substantially add to our

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knowledge base about this material's effectiveness in clinical applications.

DR. REKOW: Well, hearing no other discussion --

DR. PATTERS: One other question --

DR. REKOW: Yes, please.

DR. PATTERS: To Mr. Ulatowski, if you used Dr. Tenenbaum's labeling that this has not been shown to be superior to the OsteoGraf/N-300 have you taken it to a 510(k) device, saying it is just another hydroxyapatite, not shown to be different than any other?

MR. ULATOWSKI: That may well be the case. Hypothetically, yes, it is a possibility.

DR. PATTERS: On the other hand, if we approve the PMA as it is it becomes a predicate device for others. Correct?

MR. ULATOWSKI: No, every PMA has to stand on its own. There is no linkage.

DR. PATTERS: But, for instance, if we were to approve it and classify it in Class II, other devices can come in as 510(k)?

MR. ULATOWSKI: If you approve it as a 510(k).

DR. PATTERS: No, as a PMA.

MR. ULATOWSKI: As a PMA it is not a predicate.

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The next "me too" product has to go through a PMA and so on and so forth.

DR. PATTERS: Even if they are Class II devices?

MR. ULATOWSKI: Well, it wouldn't be a Class II. A PMA is a Class III device.

DR. REKOW: Okay, I am going to be courageous and try to restate the recommendation -- yes, Tim?

MR. ULATOWSKI: Just a last point, the Panel has to bite the bullet, given the labeling here or some construction that someone can come up with, whether there is enough to say yea or nay.

DR. TENENBAUM: Well, there is a motion on the floor, I believe --

DR. REKOW: Yes.

DR. TENENBAUM: -- and should we not vote on it?

DR. REKOW: Yes, I was just going to call the question, and I was cranking up my courage to see if I could restate it.

DR. GLOWACKI: I would just request that this time we include what the labeling would be and what the recommendations for further data would be in it because that really is implicit.

DR. REKOW: Let me read what I thought I heard and

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see if that is sufficient for us to vote on, and it may not be our final vote; it may be one that generates another motion.

I think I heard that the recommendation is that we approve the PMA pending changes in the labeling as it relates to specific indications of CD-300 -- that the CS-300 does not demonstrate superior activity relative to the "N" material or other HA materials, and to leave references to the P-15 peptide -- that references to the P-15 peptide be changed to not refer to cell binding activity, and that postmarket changes be made -- postmarket studies be made to determine the superiority of the CS-300 material over the "N" or other HA materials. Is that the essence of what you said?

DR. TENENBAUM: That is the essence of what I said. I also indicated that should superiority of P-15 over the OsteoGraf/N not be demonstrated, then approval should be withdrawn.

MR. LARSON: Madam Chair.

DR. REKOW: Yes?

MR. LARSON: I believe also the words were "has not been shown" or something of that nature rather than "is not."

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DR. TENENBAUM: Has not been shown.

MR. LARSON: And we might also consider the sponsor's suggestion that it has not been tested. That may be too mild but we certainly wouldn't want to imply that it has been shown to not be better.

DR. REKOW: Let's try it again, that approval --

MR. LARSON: Dr. Tenenbaum expressed it twice pretty much the same way so he must have some good notes.

DR. TENENBAUM: No notes.

MR. LARSON: Well, you did it so well the second time.

DR. REKOW: Why don't you write it out and read it to us so we all have one operating model? Please.

DR. TENENBAUM: You will have to give me a couple of minutes.

DR. REKOW: Okay. Talk!

DR. TENENBAUM: The motion is that the product be deemed approvable with the following conditions: That the labeling be changed such that information is included to indicate that OsteoGraf/CS-300 has not been demonstrated to be superior to OsteoGraf/N or to other HA bone implant materials. And, further, that references to the putative cell binding activity of the P-15 peptide be removed. Then

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the third issue is that postmarket studies be carried out to confirm that P-15 peptide, in combination with HA or OsteoGraf/N-300 is superior to OsteoGraf/N-300 alone. Then I think the fourth recommendation is should these studies demonstrate that P-15 peptide in combination with N-300 is not superior to N-300 alone approval be withdrawn.

DR. PATTERS: Could I ask that you change "that P-15 peptide in combination with N-300 is superior" to "if P-15?"

DR. TENENBAUM: If it is, not that it is.

DR. AMAR: These studies should demonstrate --

(Multi-member discussion)

DR. TENENBAUM: The null hypothesis that it is not superior.

DR. PATTERS: What it says now is that we know that it is superior, now you just have to show it. We want to term it if it is superior.

DR. TENENBAUM: Right.

DR. PATTERS: Would it be "whether?"

DR. TENENBAUM: Whether, not if. Great.

DR. AMAR: To determine or to confirm?

DR. TENENBAUM: Yes, that is better too.

DR. REKOW: We have had discussion. We have a

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statement that everybody -- yes, Janine?

DR. JANOSKY: I have a question, whether the last one is something that we can do. If it is found that it is not superior, is it then possible for the approval to be withdrawn? So, really, the approval is predicated on the findings of the effect of P-15, and is that something that we can do, because that is exactly what we are saying, given the findings of the P-15 study we either approve or we don't approve, or approving and then withdrawing.

MR. ULATOWSKI: The answer is yes.

DR. JANOSKY: Yes, we can do that?

MR. ULATOWSKI: Yes.

DR. REKOW: Does somebody want to call the question? Yes?

DR. TOFE: One clarification on the postmarket studies, is that single or multiple, study or studies?

DR. PATTERS: That you negotiate with the FDA.

(Laughter)

DR. TENENBAUM: If you want to put in there studies, and put in there in brackets on the advice of the FDA. I don't know if you want to do that. Why don't you put postmarketing studies, in consultation with the FDA?

MR. LARSON: Madam Chairman, what about just

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putting parentheses around the "s" on "studies" so that we are not specifying?

DR. REKOW: I think everybody can read that. Right? We can live with this to vote on it? I will call the question. All the Panel members who are voting members who want to approve this, please signify by raising your hand.

DR. PATTERS: I think you have to take a roll call.

DR. REKOW: Okay, we will do a roll call. We will start with you, Dr. Patters.

DR. PATTERS: I am still uncomfortable about how P-15 will be described in the labeling. I know how it won't be described but I don't know how it will be described. I am still uncomfortable about it but I am willing to live with that uncomfortableness so I vote in the affirmative, to accept this recommendation uncomfortably.

DR. REKOW: Dr. Amar?

DR. AMAR: I accept the recommendation.

DR. REKOW: Dr. Stephens?

DR. STEPHENS: I vote to accept it.

DR. REKOW: Dr. Janosky?

DR. JANOSKY: Accept.

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DR. REKOW: Dr. Trummel?

DR. TRUMMEL: I share Dr. Patters' discomfort with the labeling, however, I assume that this will be a finite period of time and items three and four will clear and we will get past this dilemma one way or the other so I will vote approval.

DR. REKOW: Dr. Tenenbaum?

DR. TENENBAUM: I approve.

DR. REKOW: Dr. Glowacki?

DR. GLOWACKI: I am reluctant to not agree but I can't agree with this for two reasons. One of them is because of the absence of a specific labeling suggestion, and also because item four, to me, means that it is assumed -- I am sorry, items three and four assume that CS-300 is superior to N-300 and I don't think that there is reasonable assurance of efficacy on the basis of the information that we have. So, I am voting no.

DR. REKOW: Okay. So, the vote is "n" minus one. Six in favor and one opposed. So, I think the motion carries. Tim?

MR. ULATOWSKI: Does the transcriber need this to be restated for the written record? Has it been stated from start to finish in one fell swoop, or does it need to be

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restated for the record so that there be a complete record?

TRANSCRIBER: It came in in bits and pieces, those recommendations. It might help verify the record --

MR. ULATOWSKI: Yes, many people will read the transcript and they may not be able to make heads or tails out of how the Panel finally came out. When you read the transcript, it sometimes seems so jumbled.

DR. REKOW: I will reread it then to say that the Panel has approved six to one that the product be approved with the following conditions: First, that labeling be changed such that information is included to indicate that OsteoGraf/CS-300 has not been demonstrated to be superior to OsteoGraf/N-300 or to other HA bone implant materials.

Secondly, that references to the putative cell binding activity of the P-15 peptide be removed.

Thirdly, that a postmarket study or studies, established in consultation with the FDA, be carried out to determine whether the P-15 peptide in combination with N-300 is superior to N-300 material alone.

Fourthly, that should the study or the studies demonstrate that P-15 with N-300 is not superior to the N-300 material alone approval be withdrawn.

Thank you. I think that concludes our activities

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for today. I appreciate all of your efforts. Thank you.

(Whereupon, at 4:50 p.m., the Panel adjourned, to reconvene at 8:00 a.m., Tuesday, January 13, 1998.)