(Laughter.)

MEMBER DIAMOND: I will address my question to you first since you are already standing.

DR. COCHRAN: Thank you.

MEMBER DIAMOND: The first question, in many synthetic grafting materials, it's common in extraction sites to decorticate to provide bleeding. Was that recommended or done in this case or was that just --

DR. COCHRAN: Yes. The short answer is yes.

MEMBER DIAMOND: Okay.

DR. COCHRAN: And the reason it's done is because BMP is an osteoinductive protein. It's a differentiation agent, actually. And so the cells have to get to the site. And clearly having bony walls there, you can perforate that and allow bleeding in that area to allow the cells to get in and then have exposure to the differentiation

agent.

MEMBER DIAMOND: And then the second question, what was the cause of death for that one patient?

DR. COCHRAN: Interesting story. We were calling the patient for the normal follow-ups. And we got the husband on the phone. And we said, "Could so and so come in?"

And he said, "Well, unfortunately not. She died," like yesterday or something. It was awful. And all we actually found out was that there was a suspicion of either murder or a suicide. So we never got the final blow on that but didn't particularly want it either.

MEMBER DIAMOND: No. Understood.

And I have one question for Dr. Marx. For clarification, when you presented the secondary objectives of those sites that were functionally loaded, the percentages were not adjusted, right? Those were basically

based on the percentages of patients that -- was that based on number of implants or based on number of patients?

DR. MARX: Those percentages were based on the number of patients who were successfully implanted.

MEMBER DIAMOND: Okay. And what was the primary cause for patients that did not receive the implants?

DR. MARX: The primary cause, there were only -- of the failures in the InFuse group, there are only three related to the product. The other major group was when the surgeon went in to insert the implant. By their decision, they felt that the bone quality was such that they needed further augmentation.

Those patients actually went on to receive dental implants and had successful outcomes. But according to the rigorous criteria of the protocol, they were placed in a treatment failure group.

MEMBER DIAMOND: And the patients that did not receive implants that received autograft, what was the -- because there were a few patients that seemed not to have -- that were given the autogenous bone but not functionally loaded at the time.

DR. MARX: The patients who were failures, treatment failures, in the autograft were mainly due to sinus inflammation and infection where the graft was loss.

MEMBER DIAMOND: Okay. Thank you.

CHAIRMAN BURTON: Dr. Amar?

MEMBER AMAR: Dr. Marx, in the sinus elevation study, was there any limiting factor in regard to the size of the elevation and the size of the cavity grafted? I may have missed that. Was there a critical size defect by which recombinant BMP-2 would work and beyond that size it would not work or any size basically would be grafted and leading to bone formation?

DR. MARX: You ask a very good

question. The sinus augmentation had an exclusion criteria that the patients had to have less than six millimeters of native bone. Now, they could have as much resorption as possible, even one-millimeter residual native bone. So there was no upper limit.

So many of the patients were full sinus augmentations; in other words, a totally hyper pneumatic sinus with no dentition there. So it spanned the entire size from maybe a two-tooth loss to a full dentition loss in that quadrant.

MEMBER AMAR: Horizontally?

DR. MARX: Horizontally and --

MEMBER AMAR: What I'm concerned with is that the horizontal, not so much the vertical component, the horizontal, how big could be a defect grafted by recombinant BMP-2 and, yet, be successful.

DR. MARX: Well, from the study parameters that we know, there was no limitation. We took the largest sinus, both

horizontally and vertically. The vertical limit was as much as you needed to reflect a sinus membrane to gain a gain in bone height. The horizontal width is determined by the anatomy of the patient.

And in the pre-study practice sessions that each surgeon went through to determine a standard surgical approach, the media wall of the sinus membrane was elevated so that it spanned the entire horizontal width from the lateral wall to the media wall of the sinus. So that was not a limiting factor. You could accomplish a sinus lift in the largest sinuses with the amount of product provided.

MEMBER AMAR: And for Dr. Cochran, would that be still the same for the extraction side, although the parameters are a little bit different because you have an enclosure?

DR. COCHRAN: Yes. There were no limits to the extractions. They were

individual extraction sockets, though. But there was no limit to the size. And if you really look closely at the data, there were different total milligrams of protein that was put in each of the extraction sockets.

I think the average was something like .66 milligrams per ml in the extraction defects. In other words, there were no limits. We had no limits.

MEMBER AMAR: And all of this is related to a buccal plate being missing. Am I correct?

DR. COCHRAN: Yes. Very early in the phase I pilot trial, where we did safety, we didn't have that. We did extraction sockets that were sort of complete, if you will. And we found that those defects tend to fill sort of anyway. And so it's hard to convince anybody that you're forming bone in any sort of way.

So when we went to the dosing experiment, we did the buccal wall defect. We

found ones that were missing about half the defect. And, as you saw there, we proved that was a critical size defect.

MEMBER AMAR: Any data on palatal defect or mesial defect or distal defect as compared to a buccal defect?

DR. COCHRAN: We didn't really study that. And we were trying to keep a pretty standard extraction defect model. So we don't have that. So that was not studied.

I would assume that it would do the same thing that we saw there.

MEMBER AMAR: Thank you.

CHAIRMAN BURTON: Dr. Fleming?

MEMBER FLEMING: Dr. Cochran, that's fine. I'll ask you this. I didn't notice that there was any difference between maxillary and mandibular effectiveness data presented if I'm not mistaken. Is there any difference between applying this material in the maxilla versus the mandible?

DR. COCHRAN: You're correct in

your observation. We didn't study it in the mandible. So I really can't comment on that. Our extraction defect models were all in the maxilla from the second bicuspid forward on each side.

And I don't think we have any data on mandibles. We wouldn't assume there to be much difference there, but we didn't study it.

CHAIRMAN BURTON: Dr. Zuniga?

MEMBER ZUNIGA: Maybe you can answer this. I noticed that in the material we were given, there was a case report on an 11-year-old. And so is there any data that you have regarding safety issues in children and if this was a topic at all?

And then, secondly, you had information about tobacco. And you tried to exclude the patients who were smoking. Is there any indication there is interaction with smoking and your product?

DR. COCHRAN: Let me let somebody else answer that question. I think Dr. Marx

can do that for us better than I can.

DR. CHIN: In this particular study, there was an exclusion criteria for being above the age of maturity. And I wanted to clarify. You mentioned there was a case presented of an 11-year-old. If I'm not mistaken, that is not part of this indication now. Doe that answer the question? Thank you.

MEMBER ZUNIGA: Is there any safety data on children and its use?

DR. CHIN: That was not a part of this study.

CHAIRMAN BURTON: Dr. Chin, you might as well stay up. The Chair gets to ask questions at the end. And I have several. I really have a question which Dr. Zuniga just brushed on at that point. In your application, we were all provided with two obviously relatively large binders, pretty heavy to carry in here, by the way.

(Laughter.)

DR. CHIN: We could have provided CDs for you.

CHAIRMAN BURTON: Yes. I know. Then you've got to bring your laptop. So you've got the trade-off.

That aside, you provided -- and the lead binder for this is dated October 5th, 2006. And in that, the opening section of that is an executive summary.

And my question is that in the -- and this is because some of what we're seeing today is slightly different than what was provided to us ahead of time in that 3A has four indications in that, two of which you are bringing forward today for sinus augmentation and extraction socket augmentation.

But there were also in this two other indications, which were for vertical and horizontal alveolar augmentation and indications for cystic defect. And that case that you're discussing with the 11-year-old was the one with Dr. Zuniga.

So most of us at this point in time had reviewed material for other indications that were included in this over the last couple of weeks. However, what you presented today is actually for only two indications for that.

But you have not addressed, at least as far as I'm concerned. Is there a rationale of why you are withdrawing the other two indications given the fact that this material, very candidly, is a month old, was provided for two other indications?

DR. CHIN: Yes. I could address that. In working with the FDA, the agency, we originally had the four indications, as you indicated. And at the time you received the panel pack, the panel members received the panel pack, we were moving forward with those four.

And shortly thereafter, very shortly thereafter, more discussions were concurred with the FDA's and the agreement was

to take the two indications out that you're referring to: the cleft palate as well as the cystic defect. And that was a recommendational request upon the FDA. And some discussions did occur, unfortunately, after you received the panel pack.

CHAIRMAN BURTON: As part of that, now, you brought, actually, my next question. Actually, the two indications that were deleted were vertical and horizontal augmentation and cystic cavities.

DR. CHIN: Yes.

CHAIRMAN BURTON: In the PMA and in my assumption in the original PMA, I'm aware of this. I'm an oral surgeon, and I have known about this for a number of years, sort of being around the business.

DR. CHIN: Sure.

CHAIRMAN BURTON: But in our information that was provided, there was an original indication for its use in cleft grafting, in alveolar cleft defects. And,

interestingly enough or at least I find it interesting, that that had been entirely deleted out of the packages that were provided to us.

I mean, obviously you were not applying for it for an indication. I guess scientifically I guess I'm a little concerned. Was there something adverse in that? Because you obviously weren't bringing it forward for that. And, very candidly, you didn't provide any information whether that was successful, non-successful?

DR. CHIN: Sure.

CHAIRMAN BURTON: And I guess that might give us a view into potential problems that may exist in other populations.

DR. CHIN: Sure. Okay. Well, you highlighted an incorrect statement that I made. The two indications that were taken out right after your panel packs were provided to you were the vertical and the cystic defects.

Approximately a month before that

period of time, there were other discussions about the cleft palate data set that we provided. And that was not taken out because of any issues with the safety of it. It was asked and negotiated to take that out because, quite honestly, I believe the questions were to skeletal immaturity. It had not been studied in an immature population at that point in time except these were 190 case studies, you know, for cleft palates that we submitted until about the June time frame. So there were quite a bit of discussions with the agencies about this.

CHAIRMAN BURTON: Some of the other panel members had brought up some of the issues regarding the two indications and some slight differences between the studies. I think that one of the things that Dr. Janosky, at least my interpretation of some of her questions and some of them by the other panel members, revolve around what is in the extraction socket study.

First of all, I mean, it's based primarily upon a dosing study and not a pivotal study, which, at least in looking at the data doesn't seem to have quite the power and the strength that the other studies had because you really -- with what you were bringing forth as an indicated dosage and regimen, there are only 21 patients, which, as Dr. Janosky brought out, were really spread over 7 different institutions, with none of them having more than 5 and some of them having 1 or 2 patients.

And the bulk of the people, again, it's got an n of 92, but 34 of those were part of the original dosing studies and were extremely low dosing in terms of the .43 and a .75 milligrams.

Is there a reason why there was no pivotal study done for this particular indication? And what I'm asking is, most of the data that you are providing is basically by implication over with the sinus

augmentation as a pivotal study, rather than one specifically addressing that in the extraction augmentation?

DR. CHIN: Sure. Sure. The sinus augmentation study was considered at the time to be a more difficult and challenging model to pursue. So that was embarked upon. And then the data that resulted from the extraction socket data provided the suggestion that maybe there was not needed a pivotal study because the clinical utility, the similarities of the bone that have grown to support dental implants, and the functional loading over a period of time supported that InFuse grows bone. It allows the dental implant placement as well as functional loading over time.

And we have shown that in the presentation today to show the similarities with those evidence of density, density and histology and CAT scans.

CHAIRMAN BURTON: Was there ever

any consideration given to doing any type of pivotal study in the extraction socket indication?

DR. CHIN: If I could get back with you on that particular answer because this study and activities were conducted by a previous sponsor? And my understanding is that there were not, but let me verify that for you, please.

CHAIRMAN BURTON: Okay. That would be fine. And then one other question. I guess it could be by yourself or any other. One of the things that I picked up in the augmentation as one of the facts was that the autogenous component of that was the only harvest site from the genial area.

And the reason I ask, because there was a lot of pain, neurosensory changes in terms of both short and long-term complications; whereas, there are other intraoral sites with lower morbidities than that particular area that would be

appropriate, not that that's a huge issue. It's just some of the complication rate differentials really hinge around where that donor site was and my assumption looking at your data that that was the only site. Is that correct?

DR. CHIN: Dr. Marx can answer.

DR. MARX: Once again, per protocol, the harvest site was at the discretion of the individual investigator dependent on their assessment of the size of the sinus and the needs of the graph material; that is, according to volume.

About one-third came from the iliac crest. A little over one-third came from the tibial plateau because many of these were very large sinuses that required that much bone graft volume. A little less than one-third came from the intraoral site, of which, once again, the investigator had the choice of which oral site to use.

The individuals who took oral bone

almost all took it from the chin. There was none that were taken from the ramus or the tuberosity, which are the other sites, mainly because those quantitatively don't have enough bone for most of the patients, who, remember, had an inclusion criteria, had to have less than six millimeters of bone. Therefore, these are relatively large sinus grafts. And the tuberosity and the ramus usually do not have enough quantity of bone for that purpose.

CHAIRMAN BURTON: Thank you very much.

Are there any other questions from the panel members at this time?

(No response.)

CHAIRMAN BURTON: At this point, actually, we are slightly behind schedule. But at this point we will take a 15-minute break. I've got 10:28. So we will reconvene in this room at just before 10:45. Thank you very much.

(Whereupon, the foregoing matter

went off the record at 10:27 a.m. and went back on the record at 10:45 a.m.)

DR. BURTON: Again, if we could take our seats, please, we'd like to get started.

Continuing with our agenda, we will now be going into the FDA presentation portion. They will be giving their presentations on this PMA. And the first of the FDA presenters is Dr. Robert Betz.

Dr. Betz?

DR. BETZ: Good morning. Today, FDA is asking you for your input on a new PMA for two indications for use for the infused bone graft.

Our presentation today will cover the following: preclinical studies, a statistical analysis, and a review of the clinical studies. Because a sponsor has already covered this information, our presentation will concentrate on FDA's analysis of the data.

First off, Dr. Peter Hudson will present information on preclinical studies.

Dr. Hudson?

DR. HUDSON: Hello. I am Peter Hudson. I'm a reviewer in the Division of General Restorative and Neurological Devices. I review the preclinical information of the application.

My talk will be divided into sections on device description, manufacturing, toxicology, biocompatibility evaluations, preclinical proof of concept evaluations and summaries of the preclinical effectiveness and safety information.

The product consists of recombinant human bone morphogenetic protein 2 or HBP2 to be used with an absorbable collagen sponge. The product has been approved by FDA for spinal fusion in tibia repair procedures previously. The product is identical to the product reviewed for the spinal fusion in tibia repair indications in terms of the

manufacturing process and the product itself.

The infused bone graft contains lyophilized rhBMP-2, absorbable collagen sponge obtained from Integral Life Sciences, USP grade sterile water and syringes and needles used to reconstitution of the protein. The kits are provided in small, medium, large and large two formats depending on the anatomic site to be repaired.

The small and medium kits contain 4.2 milligrams rhBMP-2. The small contain -- the small kit contains two sponges in the medium four sponges. The large and large two kits contain 12 milligrams rhBMP-2. The large kit has six collagen sponges, whereas the large two kit delivers 12 milligrams rhBMP-2 on one sponge.

The reconstituted rhBMP-2 solution contains ingredients that are typical protein buffer constituents.

RhBMP-2 is secreted by transfected CHO cells containing the human BMP-2 gene

sequence. The cells are grown in standards bio-reactor in vitro settings and the condition media is processed through a number of steps including column chromatography purifications and filtration steps.

The protein manufacturing process is identical to that reviewed for the other rhBMP-2 PMA-approved uses. Collaborative review of the manufacturing process was coordinated with CEDR reviewers.

With regard to manufacturing safety, the sponsor has conducted adequate viral inactivation validation of their manufacturing process. The sponsor has conducted these evaluations in accordance with ICH guidance for viral safety evaluations in human and animal cell lines.

The testing also included standard microplasma, viral, retroviral and sterility evaluations. FDA has reviewed this information, concluded that the process adequately addresses safety concerns, safety

issues regarding potential viral transmission concerns.

The sponsor has conducted the standard biocompatibility evaluations for a permanently implanted medical device. FDA has reviewed the biocompatibility studies and found them adequate in assessing the safety of the device. However, previously additional safety concerns were raised in review of the PMAs for spinal fusion in tibia repair.

Because BMP-2 is known to stimulate and/or inhibit cell proliferation and to affect cell differentiation, FDA in the 2002 Orthopedics Devices Advisory Panel recommended that the sponsor conduct evaluations for the potential of the protein to stimulate of the proliferation of transformed cells. The sponsor has performed those evaluations and the studies have not raised new concerns. FDA believes the sponsor has adequately addressed the post-approval study recommendations.

The sponsor has conducted an extensive series of preclinical evaluations for proof of concept determination. The studies were predominantly done in the dog and with the device design intended for clinical evaluation. That is, rhBMP-2 absorbed onto a collagen sponge. The concentrations may have differed, however, the device design was the same.

The studies were conducted in two phases from my perspective, critically sized, defect repair alone, and defect repair with subsequent implant placement.

In the first phase of testing, the sponsor investigated a potential of the device to repair critically sized mandibular defects of acute and chronic standing. They also investigated whether rhBMP-2 would work with guided bone regeneration materials. And we sought to determine the effect of other materials such as demineralized bone matrix or hydroxylapatite on rhBMP-2 induction of bone.

In addition, they conducted a limited dosing study in a nonhuman primate model.

In general, the sponsor found that bone formation due to the device was characterized by neovascularization, cellular differentiation and woven trabecular bone formation. RhBMP-2 induced bone formation in the canine jaw and in other models occurs via an intramembranous pathway without chondrogenesis.

In initial guided bone regeneration experiments, the sponsor observed an apparent interference in wound healing and bone repair. The bone density of the membrane assisted sites was less than rhBMP-2 induced bone without barrier membrane, suggesting that preservation of space might allow for bone formation more similar in nature to native bone. They also noted wounded dehiscence infection in GBR-treated dogs.

Next, the sponsor investigated the effects of biomaterial supplementation on

rhBMP-2 bone induction. In these evaluations, bilateral, alveolar ridged defects in the premolar areas in dogs were created. The sites were allowed to heal for eight weeks prior to implantation with the rhBMP-2 device. They observed a two-fold augmentation of rhBMP-2 induced bone formation with bioactive glass in DBM.

In the second chronic dog model, eight-week-old defect sites were implanted with rhBMP-2 or rhBMP-2 plus hydroxylapatite or HA. They observed significant new bone formation in sites treated with rhBMP-2 and HA in contrast to rhBMP-2 treatment alone. The investigators concluded that HA provided adequate space for new bone formation.

The bone formed with the HA product, however, it was devoid of osteoclastic activity. The bone itself was devoid of osteoclastic activity, leading the investigators to also conclude the study's preservation for rhBMP-2 bone formation was

important but the choice and use of bi-materials for space preservation was equally important.

The sponsor conducted a limited dosing study in a critically sized mandibular defect, nonhuman primate model. The study was conducted to confirm rhBMP-2 doses used in previous dog studies. They investigated just two doses, a low dose of 0.2 milligrams per mil and a high dose of 0.8 milligrams per mil. They found more consistent in even bone formation with a higher dose, but more importantly, no excessive bone formation occurred with either dose. The potential for ectopic bone formation with rhBMP-2 has been a safety concern.

In experiments that I consider second phase, proof of principle evaluation, the sponsor conducted staged experimental models. In the first stage, a defect was created in the alveolar ridge and treated with rhBMP-2. In the second stage of the

experiment, after bone formation was allowed to occur, dental implants were placed in the newly formed bone and investigated for osseointegration. The sponsor used a dog alveolar ridge defect model with subsequent implant insertion in the first study.

Defects were created and immediately implanted with rhBMP-2. Some defects received ePTFE barrier membrane or a resorbable membrane as covers for preservation of space. Healing was allowed to progress for three months. Dental implants were then placed and after an additional four months of osseointegration, prosthetic reconstruction devices, bridges, were placed. Animals were then functionally loaded for 12 months.

The results showed that a number of implants were lost due to room failure infection. Oval-shaped radiolucent voids within the newly formed bone were observed in several sites at one month, but over time, resolved. Thirteen of 24 defect sites were

noted to have bone voids. Comparable bone contact osseointegration was observed for rhBMP-2 treated sites and control -- for control resident bone-implanted sites.

The model demonstrates that the device conformed bone and critically-sized mandibular defects and that dental implants placed in these sites appeared to be functionally effective.

Localized swelling, correlated with rhBMP-2 treatment in bone voids or seromas were noted, but resolved over time. GBR again was seen to complicate wound healing in bone repair.

In another canine evaluation, a macroporous ePTFE was used in an evaluation of rhBMP-2 induced bone repair in implant fixation. The device was evaluate for repair of rich defects as an onlay in conjunction with a variomembrane.

Also, periodontal defects created were treated with a device and implanted with

dental implants. The barrier was used to cover the dental implants and the rhBMP-2 device after immediate placement.

The purpose of the experiment, in addition to investigating GER-rhBMP-2 bone formation was determined at periodontal ligaments could appropriately attach to the newly-formed bone.

The results show that bone formation in terms of area was enhanced by the barrier and defects receiving rhBMP-2 in comparison to the controls. Bone density was greater in sites receiving bone for control alone. However, the bone area was much reduced.

A conclusion drawn from these observations is that rhBMP-2 GBR induced bone is similar in quality to normal bone. The ePTFE membrane preserves space for the bone formation process to occur.

In summary, for this experiment, ankylosis of bone impact contact was found in

rhBMP-2 treated sites, but not in controlled sites. Seroma formation was noted only for the rhBMP-2 treated sites. Functionally oriented periodontal ligaments were observed in controlled impacts, but were not found within the rhBMP-2 sites. Ankylosis was believed to interfere with ligament formation.

RhBMP-2 induced bone formation was enhanced with the use of the macroporous barrier membrane.

Other investigations that the sponsor has conducted looked into the effect of rhBMP-2 on sinus for augmentation in goats, subantral augmentation in nonhuman primates in which a two-stage defect repair dental implant assessment was conducted in a nonhuman primate extraction sought evaluation.

In the goat study, new bone formation was observed at all follow-up evaluations demonstrating that rhBMP-2 can induce bone formation in the maxillary sinus. In the subantral augmentation study, newly

formed bone of similar quality to native bone resulted in equivalent osseointegration dental implants in comparison to native bone.

And in the extraction socket, nonhuman primate study, seven of eight treated sites exhibited osseointegration of the dental implants in contrast to just four of eight control animals.

In summary, for the preclinical studies, in summary, the preclinical effectiveness assessments, rhBMP-2 is found to cause bone formation in surgically-created mandibular alveolar rich defects. This effect was seen across the animal models which included dogs and nonhuman primates.

When endosseous dental implants were placed in LBR rich defects filled with RFB-induced bone, comparable bone impact osseointegration was observed at the sites. That is, comparable to native resident bone implant osseointegration.

IN summary, the preclinical study

safety evaluations, rhBMP-2 and GBR performance have mixed results. Preservation of the space may assist bone formation, however, complications were also observed.

RhBMP-2 is noted to cause localized swelling. And rhBMP-2 induced bone formation was associated with bone voids or seroma formation.

I want to thank you for your attention. And now I'd like to introduce Dr. Zhang who will review the statistical information of the application.

DR. ZHANG: Thank you, Dr. Hudson. Good morning. My name is Zhiwei Zhang and I am a statistician at CDRH FDA.

I am going to present a statistical perspective on the evaluation of InFuse bone graft.

Here is the outline of my presentation. I begin with a brief description of the device which is indicated for sinus augmentation and extraction socket

augmentation.

For the sinus indication, we have data from a dosing study as well as a pivotal study and the sponsor would like to combine data from both studies.

What I am going to do is describe the two studies, compare them for polling purposes and present results based on the pivotal study alone as well as the two studies combined.

For the extraction socket indication, all available data comes from a dosing study and I'm going to present this data later on.

The subject device of this PMA is InFuse bone graft which consists of recombinant human bone morphogenetic protein two placed on absorbable collagen sponge. This will be abbreviated as BMP.

The intended concentration for routine use is 1.5 milligram per mil. This will be the default value when I talk about

BMP without specifying the concentration. I will specify the concentration when we see lower concentrations of BMP applied in dosing studies.

The dosing studies for sinus involves 48 patients at six sites. There were three arms, an active control arm for bone graft; a low-dose arm for .75 milligram per mil BMP and a high-dose arm for 1.5 milligram per mil BMP.

Patients were randomized in such a way that all three arms were expected to be roughly equal in size.

The treatment course consisted of three phases. It began with the initial study, either bone graft or placement of a study device. And then entered the bone induction phase. Next, then two implants were placed where sufficient bone appeared to exist as judged by the investigator.

Then the treatment entered the osseointegration phase. This was followed by

functional loading image. The prosthesis was placed. And finally, in a functional restoration phase, patients were monitored every half year.

The dosing study apparently led to fuller interest in the high-dose 1.5 milligram per mil BMP. Following the dosing study, there was a pivotal study comparing 1.5 milligram per mil BMP with bone graft. The study population consisted of candidates for two states, bilateral or unilateral maxillary sinus augmentation procedure.

The pivotal study was designed as follows: 160 patients were to be enrolled at 20 sites and randomized at 1:1 ration to receive either BMP or bone graft. The study would be open labeled because treatment assignments could not be blinded.

The treatment course was similar to that of the dosing study. The primary endpoint was defined as the proportion of patients in the BMP group who successfully

received functional loading and remained loaded at six months after loading.

The protocol included in the PMA, contains a success criterion that requires the observed success rate at six months post loading to exceed 73 percent. The rationale for this criteria is unclear because the protocol was developed a long time ago with a different sponsor.

Note that this criterion involves the observed success rate in the sample and not the true rate in the population, so this is not a statistical hypothesis and a statistical justification appears lacking.

Furthermore, this criterion does not involve a comparison to the control which is odd in a randomized controlled study.

In the end, 160 patients were enrolled and randomized; 78 to the bone graft group and 82 to the BMP group. Sixty-nine patients in the bone graft group and 57 in the BMP group remained successful throughout the

entire study period.

Seven patients in the bone graft group and 18 in the BMP group failed at various points in the treatment course. For the purpose of this study, they are considered failures, even thought they may have overcome the hurdle with additional effort.

Two patients in the bone graft group and seven in the BMP group were discontinued which means they have been successful all along until they were withdrawn or lost to followup.

The two arms have been compared with respect to demographic and baseline characteristics such as age, gender and race. In this comparison, age is treated both as a continuous variable and as a categorical variable using 65 years as a cut off. That turned out to a be a significantly higher proportion of subjects who were at least 65 years of age in the BMP group than in the bone graft group. There was also a higher

proportion of male subjects in the BMP group than in the bone graft group.

For all other variables, including continuous age, the difference is between groups were not statistically significant.

The sponsor is proposing to combine data from the dosing and pivotal studies for sinus. For this purpose, the two studies are compared with respect to study population, treatment and outcomes. Similar inclusion/exclusion criteria were applied in the two studies and the patients appeared similar in terms of demographic and baseline characteristics.

The treatment courses were similar too, except for the timing of post-operative CT scans. In the dosing studies, CT scans were taken at baseline and four months after the initial study, whereas in the pivotal study, they were taken at baseline and six months after the initial study.

Similar outcomes were observed in

the two studies, although there were notable differences with respect to the change in bone height which was measured by CT scan. The difference is did not reach the usual level or statistical significance.

Overall, a major statistical issue has not been identified, including the two studies for the analysis of successful functional restoration.

Now let's look at the patients success rates at six months post-loading. Following the protocol, patients who were discontinued before or within six months of functional loading were excluded from the analysis. Now, these continual patients here at six months post loading, then in the patient accountability table presented earlier, which covers the entire study period after 24 months post loading.

Two sets of results are being presented here; one based on the pivotal study alone and the other on the two studies

combined. Recall that the dosing study had three arms: bone graft, low dose and high dose. The low dose arm is not used when the two studies are combined. And the bone graft and high dose arms were merged with the corresponding arms of the pivotal site.

In each analysis, we see here the observed success rates for bone graft and EMP as well as their difference and in the next line we see 95 percent confidence intervals for the BMP success rate and the difference. The confidence intervals for BMP were reported by the sponsor, but the sponsor did not present confident intervals for the difference between BMP and bone graft.

We prefer to make inferences about the difference between the two success rates which we believe is more straightforward to interpret.

The results of the two analyses are fairly consistent. In both analysis, the observed success rate in a BMP group is about

79 percent and in particular, meets the success criteria of 73 percent in the protocol.

On the other hand, in both analyses, the entire confidence interval for the difference lies below zero. The upper limit is close to zero, but the lower limit is below minus 20 percent. So in summary, the success criteria in the protocol is matched. However, the data shows that BMP could be inferior to bone graft by as much as 20 percent in terms of successful functional restoration at six months. So these are the main findings concerning the sinus augmentation indication.

The extraction socket augmentation indication is based on one study, a dosing study. According to the protocol, the primary objectives of the study were to estimate the success rate for dental implant placement and to find the right dose to use. The study population consisted of candidates for two-

stage local alveolar ridge augmentation procedure for buccal wall defects.

The study enrolled 80 patients who were randomized into four arms with equal probabilities. There was a no treatment group which received nothing to help grow bone and there was a placebo group which received the observable collagen sponge without any BMP in it.

In the other two arms, BMP was applied in different concentrations: .75 and 1.5 milligram per mil.

In the last three groups which received the observable collagen sponge with or without BMP, the concentration of BMP in the sponge was unknown to the patient and the investigator. In contrast, assignment to the no treatment group could not be blinded. The treatment course in this study was similar to those of the sinus studies.

There are issues in the analysis of this study for the purpose of demonstrating

safety and effectiveness. Because the study was not designed as a confirmatory study, a prospective analysis plan is not available in the protocol for the evaluation of long-term effectiveness.

So the analysis would have to be retrospective, now that the study is done and the data is in. It is generally difficult to maintain objectivity and scientific rigor in a retrospective analysis. That's why a separate pivotal study is literally required in the evaluation of medical device. So we have reservations about this retrospective approach in general.

Now, if we were to conduct a retrospective analysis where we would need to determine the appropriate control group and the primary end point, there are some controversies here. The sponsor proposed to use the no treatment group as the control group. We believe that the placebo group is more appropriate as a control.

Recall that assignment to the no treatment group was known to the patient and the investigator, while in the other three groups the concentration of BMP was unknown. A comparison of BMP with placebo is, in effect, double blinded, while comparison of BMP with no treatment is not blinded and may be biased.

The sponsor pointed out that readers of CT scans were blinded to the treatment received, but this applies only to measurements based on CT scans. It is the investigator who decided how to proceed in the treatment course and whether the patient was a success or failure.

That could help the investigator bias if, for instance the investigator felt less optimistic about patients in the no treatment group, knowing that nothing has been done to help grow bone.

The sponsor also argued that placebo has no clinical utility. While the

utility of placebo in this study is to separate the biological effect of BMP from anti-placebo effect that may exist, that's why placebo is used as a control in many clinical studies of drugs and devices even in therapeutic areas where doctors don't normally prescribe placebo as an alternative treatment.

Now disagreements over the primary endpoint as well, the sponsor proposed to treat as primary endpoints changes in bone height and width and the success rates for dental implant placement without additional augmentation.

We believe that it's more appropriate to look at the success rate at six months post loading as the only primary end point. This end point takes into account a long-term performance of the device which is not reflected in the sponsor's primary endpoints.

In fact, the ability to reflect long-term performance was cited as the main

reason for using the same endpoint as the primary endpoint in the pivotal study for sinus. Our suggestion for the primary endpoint is consistent with our evaluation for the sinus argumentation indication.

Certainly, it appears arbitrary to define endpoints after the study is done, knowing the precise result of each possible analysis. This kind of arbitrariness is inherent in this retrospective approach and can only be avoided with a well-designed pivotal study with pre-specified study hypothesis which we strongly recommend.

For the dosing study at hand, if a retrospective analysis was to be conducted, we feel that using the same primary endpoint as in the sinus study would minimize the sense of arbitrariness.

This table describes patient disposition at six months after functional loading. Of the 80 patients enrolled in the study, 17 were randomized to the placebo group

and to the BMP group. At six months postloading, 7 patients in the placebo group and 14 in the BMP group were successful. Another seven patients in the placebo group and five in the BMP group were known to have failed.

In addition, three patients in the placebo group and two in the BMP group were discontinued, meaning they were withdrawn or lost to follow-up prior to six months post-loading.

Because the study was not designed to be confirmatory, the protocol did not specify how to handle the discontinued patients which introduces some additional arbitrariness. Without a pre-specified mechanism for handling missing data, a sensitive analysis seems to be a sensible approach.

Here, we considered two methods for dealing with missing data. The first method simply treats all missing outcomes as

failures. The second method is a so-called complete case analysis which ignores the discontinued patients by assuming that the missing outcomes are missing completely at random. Using each method, we estimate the success rate at six months post-loading in each treatment group as well as the difference between groups.

IN each case, a treatment difference of roughly 20 percent is observed. In addition to point estimates, we present here confidence intervals for the treatment effect. Both intervals are very wide, spanning over 60 percentage points, so neither interval is very informative.

Because both confidence intervals include zero, the treatment effect is not significant to superiority tests. Overall, these results indicate that there is not sufficient evidence at BMP is superior to placebo in terms of six months functional restoration.

In summary, we find it difficult to interpret the results of this dosing study in objective and vigorous manner to establish the safety and effectiveness of BMP for extraction socket augmentation. The controversies over the control group and the primary endpoint, in fact, illustrate the difficulties. If a retrospective analysis were to be conducted, we believe that the approach that was suggested is more defensible than the sponsor's approach.

Next, Dr. Betz is going to present a clinical perspective.

DR. BETZ: Thank you, Dr. Zhang. At this time, the standard of care for integral bone grafting is the autogenous bone graft. Alternatives include the allograft from the same species; the heterograft from other species; and the alloplast, an inert or synthetic bone grafting material. It is well known in the dental community that there is significant patient morbidity associated with

harvesting autogenous bone whether it be from intra-aural or ex-aural sites.

The sponsors proposing the use of infuse as an alternative to autogenous bone grafting, their proposed indication for use statement presently states that infuse is indicated as an alternative to autograft from maxillary sinus simultaneous procedures and localized alveolar ridge augmentation for bone defects to the extraction sites.

Most alveolar ridge augmentations and sinus augmentation procedures are performed in preparation for the placement of endogenous dental implants.

Study documentation includes information from both indications for use. The main support for these indications was in the form of three clinical studies: the sinus augmentation dosing study, the sinus argumentation pivotal study and the extraction site dosing study.

Supporting these studies were a

report of adverse events and risk analysis. The sponsor also submitted an analysis of pool data.

As stated previously in our statistical presentation, the sinus argumentation indication for use is supported by the pivotal study and the pooling of dosing and pivotal data. The manufacturer saw to demonstrate functional loading of implants at six months after implant placement. In the pivotal study and the pool data, combined, about 80 percent of the patients receiving the infused had dental implants that were successfully loaded for six months.

About 90 percent of the patients in the autograft control group had successfully loaded dental implants for six months. These results suggest that the device did not perform as well as autograft. The sponsor met a success criteria using sample size calculations, but the infused did not perform as well as the control group.

Dr. Zhang indicated that infused may be inferior to autograft by a margin of up to 20 percent. However, bone was regenerated in a quantity and qualify sufficient enough to support dental implants.

For the extraction site indication, there was no pivotal study. The only study that we can truly rely on is a small extraction site dose escalation study evaluating the response of alveolar ridge to implantation of infuse. As Dr. Zhang stated, the retrospective analysis of this data may not be rigorous enough to support this indication for use.

In this study, the sponsor reported that the ridge height extraction sites remained at pre-extraction levels. He also reported that there was increase in alveolar ridge with and that dental implants were able to be placed without original additional ridge augmentation procedures.

The sponsor also stated that 18

out of 21 dental implants treated with a larger dose of implants, infuse, were successfully loaded for six months.

It was also noted that the known treatment control group produced some increase in ridge width. This is contrary to what is expected clinically, generally after a tooth is extracted untreated alveolar ridge experiences bone absorption in both the horizontal and vertical dimensions. This aberration is unexplained at this time.

The sponsor states at the extraction site data is enhanced through clinical similarity to the sinus argumentation data with respect to location and procedures. It should be noted that extraction sockets will spontaneously heal with bone and a pneumatized maxillary sinus will not.

Analysis of the adverse events may give us insights into the safety profile of infuse as compared to autograft. We will discuss surgical adverse events and antibody

responses for both autograft and infuse.

There were many reported adverse events. However, there were no serious adverse events reported that were specifically related to the use of infuse. Although ectopic bone had been a concern in preclinical and orthopedic studies, where infuse was used, there were no basis of ectopic or exuberant bone formation reported with intra-oral use of infuse.

This table compares the number of patients having adverse events for both groups. The total number of adverse events were greater for autograft than for infuse. This is to be expected when autonomous bone is harvested. Of particular note is the gate disturbance events reported for autograft. Not mentioned in the original table is the adverse event sensory loss. This was in a subsequent table by itself. This occurred in greater than 10 percent in autograft patients by themselves. This supports this data, this

whole table supports the sponsor's claim related to reduced morbidity associated with the use of infuse.

Not reflected in this table is the observation that there were more patients that reported facial edema with infuse in the maxillary sinus than with autograft. However, overall, facial edema results for the combination of sinus and extraction site data did not reach statistical significance.

Oral edema was greater when infuse was used than in the autograft group. This too was not statistically significant. Results of swelling associated with infuse appeared to be consistent with reports of infuse edema present in orthopedic studies.

Mouth pain for both groups appeared to be quite similar.

Amendment 007 to this PMA reported on 184 patients that were evaluated for antibodies. Two point two percent of the infuse patients had developed anti-rhBMP-2

antibodies, while none of the autograft patients had developed these antibodies.

The presence of antibodies to rhBMP-2 were not associated with immune and mediated events such as allergic reactions. Antibody response to infuse should be considered to be an adverse event even though allergic responses were not a clinical factor in treating patients.

Subsequent antigen challenge effects and neutralizing capacity of antibodies to infuse are not known. Twenty percent of the infused patients had anti-bovine type 1 collagen antibodies, while 31 percent of the control patients developed these antibodies.

This appears to be an unusual result because autografts did not contain bovine collagen and baseline studies indicated that only about four percent of the general population exhibit antibody response to type 1 bovine collagen.

It should be noted, however, that the antibody responses to infuse, observed in the study, are in line with antibody responses observed in previously proved infuse spinal fusion studies. The significance of the control group antibody response is not explained.

Most importantly, none of the patients from either group developed anti-human type 1 collagen antibodies.

This table and the one to follow outline the risks and benefits that the sponsor identified in the PMA for infused and autograft. This table outlines the risks that the sponsor has identified. Most of the risks for infuse are associated with potential interactions between the patient's immune system and infuse such as unknown effect on mother's milk, unknown effect on fetal development and reaction to subsequent immune system challenge.

Risks associated with autograft

are related to the possibility that the patient may not have bone available in quantity or quality sufficient enough for harvesting an engraftment. There is also the morbidity associated with the harvesting of that bone.

This table outlines the benefits that the sponsor identified in the PMA for infused and autograft. Most of the benefits of using infused are related to the reduction and morbidity associated with not having to harvest autogenous bone and the ability to have a readily available source of bone grafting material.

Benefits for autograft are that it's the standard of care, the patient always carries around their own donor bone and the allergic reactions should be nonexistent. You will be asked to use your clinical experience in considering the risks and benefits of the use of infuse in your discussions and deliberations.

In summary, infuse has demonstrated the ability to generate bone in the maxillary sinus. There are fewer successfully loaded implants in the infused patient group at six months. However, it should be noted that the 73 percent study success rate criterion mentioned in the sample size calculation was exceeded during the study.

There was no pivotal study submitted for the extraction site indication for use. There was also no active control group in the dosing study. In the limited number of patients evaluated, after tooth was extracted, infuse was associated with the maintenance of alveolar ridge height and increase in alveolar ridge width.

The lack of a pivotal study, the lack of active control group and the effects of the limited sample size may adversely affect the validity of conclusions drawn by the sponsor. This parallels Dr. Zhang's

statement that the retrospective analysis of this data may not be rigorous enough to support this indication for use.

In both studies, for both treatment groups, the quality and quantity of bone generated was sufficient to support the placement of endosseous dental implants. The adverse event profile for autograft was significantly different from that of infuse in the sinus augmentation study. The adverse event profiles for infuse patients in both studies were similar.

Again, it should be noted that bone in extraction site heals spontaneously and bone in its pneumatized maxillary sinuses does not. Therefore, the bone in these recipient sites may respond to infuse in different ways. Extrapolation of data -- extrapolation of extraction site data to the sinus augmentation study and vice versa may introduce confounding factors that may affect the conclusions drawn. You will be asked to

consider the statistical validity of this data in your discussions of the clinical validity of the analysis of these data.

Thank you.

DR. BURTON: Thank you, Dr. Betz. At this time I'd like to ask the panel if they have any points of clarification from the presentations from any of those individuals.

Dr. Janosky.

DR. JANOSKY: Yes. I heard mixed messages and I was hoping for clarification. I heard one time it was said that the criterion for 73 was based on an a priori sample size calculation and then I hard another series of statements that said that there was no known justification for that number.

Am I correct in that there's some confusion or did I miss interpret what was being said?

DR. BURTON: Dr. Zhang?

DR. ZHANG: The percent of 73

percent, it was used in the sample size calculation. It was the assumed rate for -- in the calculation to justify the proposed sample size.

Other than that, I have not seen a real statistical justification for the success criteria.

DR. JANOSKY: Dr. Burton, can I continue with a few more questions?

DR. BURTON: Yes, please do .

DR. JANOSKY: Would you provide more detail as to what were the other parameters for that 73 percent?

Because was it based on the pivotal study? Was it based on the dosing study? I'm trying to get a handle on sort of the appropriateness of that criterion, especially across the various studies. That's where this line of questioning is coming from.

DR. ZHANG: the only information that's available to me is from the protocol I saw and in the protocol, basically, the

protocol suggested that 70 percent would be -- was considered by some clinicians to be a cutoff point and then they went ahead and suggested 73 percent.

There was really no statistical justification for this 73 percent. As I said there were no statistical hypotheses.

DR. JANOSKY: Can I please ask another series of questions?

DR. BURTON: Yes.

DR. JANOSKY: Dr. Zhang, I'm trying to get a handle again on another issue and this issue is what actually was pooling of data. And sort of the appropriateness of that approach.

If I take a look at the data that are presented for the pivotal study and I look at the data that you had presented and also the sponsor had presented, what were the N that contributed to those data points?

DR. ZHANG: When you say pooling, do you mean pooling the two studies?

DR. JANOSKY: Exactly. What I'm looking at right now is what you had presented to us and the sponsor had done something very similar. This looks like -- it's a slide on page 15. I don't know how that corresponds to what you have there.

DR. BURTON: Fifteen in the FDA presentation?

DR. JANOSKY: Exactly. It's in the pooling studies and the slide is entitled "Patient Success Rate at Six Months Post Loading."

What I'm concerned with is that the data were summarized and they weren't weighted. And what would be the difference if they were weighted? That's sort of the issue that I'm trying to get at. What was the N that contributed to the pivotal study? What was the N that contributed to the dosing study? And were these truly polled data or where weighting was taken into account, given the different Ns or were those, in fact,

summarized and added dated, where the difference in the Ns were not taken into account and if that's the case, what actually are those success rates?

So within the pivotal study, the N is approximately for BMP, approximately 80?

DR. ZHANG: Yes.

DR. JANOSKY: Eighty. Okay, and then for the dosing study for BMP, the N is approximately --

DR. ZHANG: Sixteen.

DR. JANOSKY: Okay, so that the number that we see there which is 79.6 under BMP for pivotal plus dosing, was that a weighted average so that we take into account those different sample sizes and the contribution each of those studies had? Or was that a summation?

DR. ZHANG: It can be seen as a weighted average because well, when the two studies are pooled, when the patients are simply combined for each group for each

treatment group, and then the success rate is calculated, so it can be regarded as a weighted average of the observed success rates in the two studies, whereas the sample size being the rate.

DR. JANOSKY: And just one follow-up question, please.

Dr. Burton, is that okay?

Of concern to me is that the dosing study is about one-fourth the size of the pivotal study. So simply combining those success rates is letting that success rate for BMP to be overridden by the pivotal study and if that is the case which, in fact, it is, if you look at these data, which way did that bias the results?

That's the second issue that I'm trying to get at is that when you have these polled data, it's actually driven by the pivotal study and not the dosing study. And did that provide for a more conservative estimate or a less conservative estimate?

That's the issue that I'm trying to tease apart.

DR. ZHANG: Numerically, if we look at the results, we see that after combining the two studies, the success rate for BMP is slightly higher, but the difference is very small. When we do the weight -- we are not aware of any systematic bias that makes this or we wouldn't have done this at all. Before we did this, we compared the two studies, as I said, in terms of study population, treatment and outcomes. And the two studies did appear to be similar to each other, especially in terms of functional restoration.

DR. BURTON: Any other questions? Thank you, Dr. Zhang.

Dr. Chin, you had raised your hand earlier, did you care to make a response at this time? You'll have opportunities later, if you care to take a little more time. I just want to offer that to you now.

Dr. Gunter?

DR. GUNTER: Thank you. A couple questions for the FDA. One, getting back to the 73 percent number. My understanding is that was something that was submitted in a protocol to the IDE.

So my question is was there discussion with the FDA about the acceptability of this criterion before this study began? Was there any kind of agreement with the FDA? And can you shed any light on that, please?

DR. BURTON: Dr. Betz?

DR. BETZ: It was approved in the protocol, yes.

DR. BURTON: Can you give us any more idea exactly where that 73 percent came up from?

DR. BETZ: It's my understanding that they asked experts, correct me if I'm wrong, they asked their experts and they used previous studies to come up with a 70 percent

and I'm guessing that the 73 just kind of gave them a little extra cushion.

DR. BURTON: Dr. Marx?

DR. CHIN: Dr. Marx will address this question.

DR. BETZ: Thank you.

DR. MARX: As part of the group that was in the initial inception of these studies, there were no preexisting statistically valid data to go by on success rates. So we have to pull the existing literature at the time which a group of us did. There were five of us in the initial study module, Dr. Spagnoli, myself, Dr. Nevins and Dr. Triplett. And we pulled the literature. We took that plus our own experiences and the Academy of Osseointegration Consensus Conference, which was available. And the pulled data from that indicated that a success rate of 70 percent for any product that would be inductive would be a reasonably acceptable rate. There was

nothing prior to that to go on. So we had to develop one de novo in a way.

DR. BURTON: Thank you. Any other members have any questions?

I have a couple of questions for Dr. Zhang as well. I'm sorry. I'll let Dr. Gunter go ahead, first.

DR. GUNTER: One more question. I found the slides on the risk benefit, that was helpful to put things into perspective. When I saw the slide I was thinking what about all the experience with a marketed product and I'm thinking about the antibody risks.

Has there been any post-marketing surveillance data with the marketed product to indicate that any of these risks with -- for antibody development are substantial or can you quantitate that for us in any way?

DR. HUDSON: The antibody titers continue to be compiled as Dr. Betz, we've indicated the incidence in this study was 2.2 percent which is a very low incidents and it's

in the same comparable ballpark as was seen in the spinal fusion study.

DR. BURTON: Does that answer your question?

DR. GUNTER: I guess it helps a little bit, but specifically have there been any reports, device adverse event reports, anything like that from the marketed product that would indicate that there's clinical implications from the development of these antibodies?

DR. HUDSON: There are medical device reports, but there's been no correlation to my knowledge of an immune response that's led to a clinical symptom.

DR. BURTON: Thank you. I'm sorry, Dr. Zhang, I have to apologize for sort of yo-yoing you up and done there.

In looking at some of the statistics that you reviewed, particularly in regard to the extraction site issue, is -- there are some concerns I know that Dr.

Janosky has brought up and I just would like a little more clarification if you can do that on the fact that you have a very small N of 21. It was really a dosing study and not a pivotal study.

As you said, some of these issues were built in terms of the size and the pivotal study for the sinus augmentation were driven by the number of patients included in that was larger to give it some statistical significance. Your analysis showed the fact that it was difficult or impossible to really get significance out of the extraction site data because of that. Also due to the fact that the N is small at 21, you know, again, just a little more clarification of why we just can't get any statistics out of that.

Is it small size? Is it that the variance was so great that it becomes -- again, most of what you showed was not significant statistically.

DR. ZHANG: Well, the result

certainly has to do with the sample size as well as the true effect if there is any.

If there is truly a positive treatment effect, of course, the power to reject a null hypothesis would increase with sample size. So hopefully with a bigger sample, you know the power might be greater for finding, for concluding superiority.

But this is assuming that there is a positive treatment in effect. If there is no treatment in effect, then the sample size doesn't matter, you know. The power -- well, I mean if there is no treatment in effect, then the probability that the device will be found superior to placebo remains small regardless of the sample size.

DR. BURTON: Okay, I guess this is what I'm getting at and I'm still maybe not -- I think you've explained it, but I guess I'm still not clear. Is it that in your summary you just said it was difficult to conduct a rigorous retrospective analysis to the

controversies and so we came up in your primary analysis at the six month success point -- again, there may be a positive effect. It could be either the fact that it may not even exist and in a larger sample size would not find that because it's not there. Or there may be one, but again, the sample size is so small that we cannot determine that.

DR. ZHANG: Right.

DR. BURTON: Thank you. Yes, follow up. Don't sneak off too quickly.

Dr. Amar?

DR. AMAR: What was the predicted effect size by which you would predict and give a sample size? I'm following on based on the effect size, you would give a sample size that would predict a result?

DR. ZHANG: You mean an adequate sample size which would have adequate power to conclude superiority.

We have not made any such

calculation because we simply didn't -- well, it's not clear that such a study has been planned.

DR. AMAR: Dr. Hudson, I'd like to ask you one quick question. You did mention that there were some issues with ectopic bone formation. And I suspect that there is post-surveillance with the spinal fusion study, am I correct?

DR. HUDSON: There's not post-surveillance for ectopic bone formation. And I'm sorry if that was misunderstood. Ectopic bone formation has always been a concern. That's been something that investigators have though, the cytosine can get outside of the space a little bit and maybe bone formation wouldn't be exactly where we'd want it to be.

There wasn't in the spinal fusion study, there wasn't any ectopic bone formation that was -- there was no evidence that that was a problem and so in the preclinical evaluations that they did in this -- for this

application, that was something that was looked for. Ectopic bone formation was commonly seen.

DR. AMAR: What was the percentage of ectopic bone formation observed with the spinal fusion study?

DR. HUDSON: I don't think there was anything seen -- I mean if there was one patient that would have been it. I don't even know if there was that.

I mean it's been a concern all along, but --

DR. AMAR: Conceptual or hypothetical?

DR. HUDSON: Conceptual in that the preclinical evaluations, preclinical studies in support of the spinal fusion, I think there was

-- if I remember correctly, there was ectopic bone formation seen in some of the higher doses that was used so it came outside of the site a little bit.

DR. AMAR: We could safely say that there was no ectopic bone formation irrespective of the study, spinal fusion or the study presented?

DR. HUDSON: For this study presented, yes, that's true and in the spinal fusion I don't think there was any site seen.

DR. BURTON: Thank you. Are there any other questions from the panel at this time?

Does the sponsors have any comments they'd like to make at this point?

We're getting ready to break for lunch. I just wanted to offer that opportunity. We will now go ahead and break for lunch. Please return at 12:45. Please exit the room as expeditiously as possible. It will be secured by FDA staff during this break, so please take any personal belongings you may want at this time. You will not be allowed in until we reconvene at 12:45.

You can leave things here.

(Whereupon, at 11:48 a.m., the meeting was recessed, to reconvene at 12:45 p.m.)

CHAIRMAN BURTON: Thank you all. I think everybody has taken their seats. I'd like to call this meeting back into order.

At this point, before we move on, does any of the panel members have any questions for the sponsor or the FDA at this point?

(No response.)

Okay. Seeing none, we will continue with our agenda, with the panel discussion, and Dr. Zuniga will begin the discussion with a short presentation. Dr. Zuniga.

DR. ZUNIGA: Thank you, Dr. Burton, and it's a pleasure to present to the panel my summary conclusions of the proposal. I think that the biologic and scientific merits for the application of the placement of dental implants using an osseoinductive agent

such as BMP versus an autogenous bone graft has significant merits to our profession.

And those merits can be measured in terms of clinical application and, bear with me, some societal applications. I think that the clinical applications are that if this product device supports and provides a mechanism for bone deposition that would support an implant, that is a positive benefit for our patients and our profession.

It allows us to, as physician clinicians, to point of placement provide bone support and growth to support these devices. And, importantly, it avoids bone grafting techniques and, as pointed out by the presentations, of the variable risks that are associated with those. So the risk-benefit ratio of avoiding a bone graft or a second procedure, both short term and long term, are significant.

Anyone who provides -- obtains bone grafting in patients knows that there are

significant adverse events that affect the -- those patients are subjected to that have long-term effect, both in terms of care and impacting costs.

Obviating the need for bone graft would provide ambulatory services for a large group of patients, and in a constantly aging population the -- avoiding risks, exposure risks, for the patients using this device would be very, very positive, and a societal benefit in my opinion.

The sponsors requested -- are requesting approval for this device and use in two indications, one of which is sinus augmentation. In so doing, they provided three studies of pilot dosing and pivotal studies, and their primary endpoints were the demonstration that this device would provide and induce in bone, and be able -- and that induced bone would be able to support an implant placement.

They also had secondary endpoints,

which were the -- that these implants would be able to support restorations at least 12, 18, and 24 months, and there were demonstrable new bone formation and they were able to characterize that bone.

I believe the studies did demonstrate a treatment effect, and especially in the pivotal study which was randomized and blinded, although open, because it is -- an autograft was used, that they did demonstrate bone growth of significance, although less than the autogenous bone graft. They were able to meet their success rate of 73 percent of implants that were functional.

I do share a concern that there was a small but measurable decay in the implants in the patients over the period of the study in the secondary endpoints up to 24 months. Again, as was pointed out, it's a small decay, but it was measurable, both in terms of the implant survival as well as functional restoration, which would -- I would

be supportive of continued post-market surveillance to explain if this is, in fact, a continuation.

In terms of bone quality in the secondary endpoints, I believe they were met and they are satisfactory, and I believe the secondary endpoints were also satisfactory.

In terms of safety issues, when compared to the control autograft, I believe the sponsors have demonstrated that product safety is superior. The procedures -- avoiding autograft means they are avoiding a less invasive approach, and there probably is less operating time and exposures.

And although not mentioned, I would assume that the individuals, the clinicians' experience who are experienced in placing bone grafts for sinus augmentation, do not need additional training or education, nor are the patients required to have additional education. So I think the application of this device does not increase the complexity of the

procedures and experience or the demands on the patients to have -- to go to success.

The risk-benefit ratio, again, would favor the product, at least in my opinion, over the autografts, and that's based on the adverse events recorded. And, again, there are certainly societal benefits in terms of cost and patient acceptance.

So, in conclusion, my conclusion is that the sponsor did provide reasonable assurance, as we were asked to comment on, that this device is effective for sinus augmentation, as indicated for implant placement. I believe the sponsors also demonstrated that the device is safe for this indication and that it may even provide a more positive risk-benefit purpose for our patients.

The sponsors also are requesting approval for indications in an extraction socket augmentation. The clinical application for this -- excuse me, the benefits for this

application I think are also very positive. As stated, that the standard of care does not include the routine use of autografts, or even allografts, into extraction sockets following their removal of teeth.

I do agree with that comment, so the use of an autograft in a control group is probably not indicated, and that they also demonstrated that the placement of no graft at all, or no treatment, did point out that if -- that the number of patients that were able to have an implant placed in the future were significantly less than compared when the device was used, which we know that there is a natural healing or filling in of extraction sockets following the extraction of teeth.

Therefore, the application of this device is not to provide a bone fill, but to provide support for an implant.

The no treatment group did point out that if a patient were to require -- request an implant in the future, or require

an implant in the future, that there's a greater than 60 percent chance that they will need additional autografting procedures, therefore, again, exposing them to additional risks and additional surgery and the costs of that.

The use of the device would, therefore, prevent -- potentially prevent the use of future autografts for that patient population.

Therefore, I think there is a benefit for the use of the device in this indication. However, the scientific rigors of demonstrating and improving that were less than ideal, in that the sponsors were only able to provide a pilot and a dosing study, and there was not a pivotal study which allows good, solid, scientific evidence basis for implant placement in this condition.

There is also a growing area of implant dentistry, of the placement of immediate implants into extraction sockets

directly. So there is another avenue of placement of implants without the use of such a device, not indicating that that's a future study, but one must be aware of these indications.

I believe that the sponsors did demonstrate a treatment effect in this patient population. Their endpoints were that there was a measurable change in bone height and width and that that would augment the rate of success of implant placement, and that the secondary endpoints were success of a prosthetics placement on that implant without additional augmentation requirements, and that functional loading would be preserved for 6, 12, 18, and 24 months after.

I believe that the sponsors did demonstrate that there was at least no change in bone height following the placement of the device, and they -- but they also demonstrated an increasing success rate, so there would be a correlation between the preservation of the

bone -- of the extraction socket that would support an implant. I think this was demonstrated.

They did demonstrate a greater success in that implant placement as compared to the no treatment, but I believe that a proper control in a pivotal study may provide better information regarding this, in part, as was brought up, due to the small end in the distribution and dosing differences amongst the dosing studies.

At 24 months, the functional loaded implant was about -- success rate was about 71 percent, making some concern about the stability, and, again, similar to the sinus augmentation studies, a need for a pivotal study, and at least some post-market surveillance may be necessary.

As far as safety issues regarding the augmentation or extraction augmentation studies, I believe that there are no new concerns brought up regarding the safety of

placement the device in extraction sockets and compared to the sinus augmentation study. So they are very positive.

However, I do have concerns about the application and limitation of the extraction socket studies in the maxilla. It is the assumption that the overall indications that are requested by the sponsor are for all extraction socket augmentations, and the exclusion of the mandibular studies or cases are probably -- may be trivial but not necessarily trivial. And they cannot comment about that.

For instance, in the mandible there may be special tissue effects as the device is exposed to other tissues, including nerve tissue. I do not know or cannot conclude that there were any special additional educational needs for the clinician in providing the device for extraction sockets. I might assume that it may -- this may not need additional training as compared

with the sinus augmentation, but it may require additional experience by the clinician in the placement to afford success.

So, in conclusion, I believe that the sponsor did demonstrate a treatment effect that was very positive and important for the profession, but I do not feel that they satisfied with reasonable assurance that the device is effective for the indication of extraction socket augmentation in the mouth, in the oral cavity.

I believe that the device is most likely safe, as for the indication, and may provide, again, a very positive risk-benefit ratio. But there may be some minor concerns regarding adjacent tissues or in the mandible.

Thank you.

CHAIRMAN BURTON: Thank you, Dr. Zuniga.

To guide the discussion, the FDA at this point has questions for our consideration. Dr. Betz. And I'd like to go

ahead and ask that -- the four questions, because we always tend to move a little bit independently between them, that we go ahead and present all four of the questions.

We will go through them in order in terms of the discussion process as much as possible, but I think it's good just to -- that everybody has a good chance to look at what the four questions are, because, again, there is always interaction between those.

Dr. Betz. Or, Michael, are you going to be doing this? He's going to do that. Okay. Thank you.

Dr. Betz.

DR. BETZ: Thank you. Panel question number 1 -- In the light of preclinical data, and the adverse events presented for infused, please discuss the safety of using infused for each of the proposed indications. Number 1, sinus augmentation, and, number 2, ridge augmentation at extraction sites.

Question number 2 -- An analysis of the sinus augmentation studies indicates that an infused may be up to 20 percent less effective than the standard of care, the autograft. In light of the above statistics from the FDA's statistical presentation, please discuss the clinical implications of the infused results presented in this PMA. Number 2, based on the data presented in the PMA for this indication, please discuss whether the possible reduction in morbidity associated with infused outweighs the potential reduction in effectiveness when compared to autograft. Basically, risk versus benefit.

Question number 3 -- Given the data submitted for ridge augmentation at tooth extraction sites, please discuss whether there is sufficient, valid scientific evidence for this indication to arrive at a clinically meaningful conclusion with respect to device effectiveness. Is the data submitted rigorous

enough to support this indication for use? Given the data provided, please discuss whether it is possible to evaluate the risks versus benefits of this indication.

Question number 4 -- please discuss whether sufficient, valid scientific evidence has been provided to demonstrate the safety and effectiveness of infused bone graft for the following indications requested by the sponsor -- sinus augmentation and extraction site augmentation.

We also have definitions of "safety" and "effectiveness," if you need them.

CHAIRMAN BURTON: Why don't you go ahead and present that now as well.

DR. BETZ: Okay. "Safety," according to 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific that the probably benefits to health from use of the device, for its

intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

"Effectiveness" -- there is a reasonable assurance that the device is effective when it can be determined, based upon scientific evidence, that the significant proportion -- that in a significant proportion of the target population the use of the device for its intended use and conditions of use when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results. That was scientific evidence.

According to 21 CFR 860.78)(2), indicates that valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well documented case histories conducted by qualified experts, and reports of significant

human experience with a marketed device from which it can fairly and responsibly be concluded that qualified experts that -- by qualified experts that there is a reasonable assurance of the safety and effectiveness of the device under its conditions of use.

Isolated case reports and random experience reports lacking sufficient details to permit scientific evaluation and unsubstantiated opinion are not regarded as valid scientific evidence to show safety or effectiveness.

CHAIRMAN BURTON: Thank you, Dr. Betz. Can we go back to question 1, then, and put that up on the screen? Thank you.

I'd like to open the discussion on question 1 for the panel. Again, remember, it's in light of the preclinical data and adverse events presented for infused. Please discuss the safety of using infused for each of the proposed indications -- 1, sinus augmentation, and, 2, ridge augmentation in

extraction sites.

Dr. Patters.

DR. PATTERS: Thank you, Dr. Burton. I think this question, in my mind, is the easiest one being posed to the panel, that quite clearly there is overwhelming evidence that this device appears to be safe, and the adverse reactions primarily are the result of surgical procedures. No evidence that this device increased the number of adverse reactions. As a matter of fact, the evidence is to the contrary.

So I would say that the preclinical data and the clinical data establish safety of infused, both for sinus augmentation and for ridge augmentation in extraction sites. I don't think there is any question about it.

CHAIRMAN BURTON: Thank you, Dr. Patters.

Would anyone else care to enter into a discussion on this question? Yes, Dr.

O'Brien.

DR. O'BRIEN: Since I haven't seen this procedure done, I'm assuming from what you have said that carrying the chemical, the protein, is inserted into extraction sites for a considerable length of time.

What holds it in there? Is it possible that it could be dislodged in the mouth, or is it exposed to the mouth conditions? And so, if it is dislodged, the patient swallows it, would that have any adverse effects in the GI tract?

CHAIRMAN BURTON: Let me -- I'll ask Dr. Marx, because maybe I can broaden that question out just a little bit, in the fact that one thing that hasn't been addressed was the fact that if there was any -- and I didn't really see much that talked about wound dehiscence either -- in either indication, whether that had occurred.

But I guess as something that was used more broadly, if there were dehiscences

-- and I think that that's what Dr. O'Brien would like to know -- is one would be obviously lost to the product in toto, or, in fact, let's say it does dehisce and becomes exposed to the oral cavity during, let's say, the early healing phases, how does that affect its effectiveness and potential safety?

And whoever you'd like to have, Dr. Marx or Dr. Cochran could address that.

DR. MARX: Yes. For those of you unfamiliar with the procedure, in the extraction socket surgery the product is placed into a tooth extraction socket and the gum tissue, or mycosis as we call it, is sutured over that. And so that is sealed away from the mouth cavity per se, where a patient could swallow it.

The observation of would dehiscence was very small. As an observer of this, we find that it also has a very positive effect on soft tissue healing. So it was a rare event. When it does get exposed, like