UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION

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DENTAL PRODUCTS ADVISORY PANEL

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TUESDAY,
JULY 13, 2004

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The above-entitled Meeting was conducted at 8:30 a.m., at the Hilton Washington DC North/ Gaithersburg, Salons A and B, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Jon B. Suzuki, Chairman, presiding.

PANEL MEMBERS PRESENT:

JON B. SUZUKI, DDS, PhD, MBA, Chairman, Professor at the University of Pittsburgh School of Dental Medicine

MICHAEL E. ADJODHA,MChE, Executive Secretary, Department of Health and Human Services, FDA, Center for Devices and Radiological Health, Office of Device Evaluation, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices

SALOMON AMAR, DDS, PhD, Voting Member, Professor of Periodontology at Boston University School of Dental Medicine

DAVID L. COCHRAN, DDS, PhD, Voting Member (Non-Voting for this Meeting), Professor and Chairman of Periodontology at the University of Texas Health Science Center, San Antonio

ELIZABETH S. HOWE, Consumer Representative, Outreach

Coordinator, National Foundation for Ectodermal Dysplasias, Auburn, Washington

ALLISON F. LAWTON, MBA, Drug Industry Representative, Senior Vice President of the Genzyme Corporation, Cambridge, Massachusetts

WILLIAM J. O'BRIEN, MS, PhD, Voting Member (Non-Voting for this Meeting), Professor of Materials Science at the University of Michigan School of Dentistry, Ann Arbor

DANIEL R. SCHECHTER, JD, Device Industry Representative, General Counsel for Parkell, Incorporated, Farmingdale, New York

INDER SHARMA, PhD, Consultant, Deputized to Vote, Associate Professor of Biostatistics at the Morehouse School of Medicine, Department of Community Health and Preventative Medicine, Atlanta, Georgia

DOMENICK T. ZERO, DDS, MS, Voting Member, Professor and Chairman of Preventative Dentistry at Indiana University School of Dentistry, Indianapolis

JOHN R. ZUNIGA, PhD, DMD, Voting Member, Professor and Graduate Program Director of Oral Surgery at the University of North Carolina School of Dentistry, Chapel Hill

SPONSOR PRESENTERS:

MARK CITRON, Vice President, Regulatory Affairs, BioMimetic Pharmaceuticals, Inc, Franklin, TN

ROBERT GENCO, DDS, PhD, Vice Provost, State University of New York at Buffalo

WILLIAM V. GIANNOBLE, DDS, DMSc, Associate Professor at University of Michigan

SAMUEL E. LYNCH, DMD, DMSc, President and CEO, BioMimetic Pharmaceuticals

MYRON NEVINS, DDS, Associate Professor, Harvard University

FDA PRESENTERS:

ANGELA E. BLACKWELL, MS, Biomedical Engineer, Dental Devices Branch, DHHS/FDA/CDRH/ODE

JUDY S. CHEN, MS, Mathematical Statistician (Biomedical), Division of Biostatistics, DHHS/FDA/CDRH/OSB

M. SUSAN RUNNER,DDS, MS, Captain, USPHS, Deputy Division Director, DAGID and Chief, Dental Devices Branch, DHHS/FDA/CDRH/ODE

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

8:30 a.m.

CHAIRMAN SUZUKI: The Dental Products Panel of the CDRH Medical Devices Advisory Committee. My name is Jon Suzuki. I'm serving as the Chairman of the Dental Panel. And I would like to call this meeting to order.

The Executive Secretary, Michael Adjodha, will make some introductory remarks.

Mr. Adjodha?

EXECUTIVE SECRETARY ADJODHA: Thank you, Chairman Suzuki.

My name is Michael Adjodha, Executive Secretary of the Dental Products Panel.

Allow me to introduce the members of our panel. Please raise your hand as I call your name.

The Chairman of the panel is Dr. Jon B. Suzuki. Chairman Suzuki is a periodontist and immunologist, and is the Associate Dean of the School of Dental Medicine at Temple University in Philadelphia, Pennsylvania. Note that change from the agenda. This change is recent.

Joining him are the following panel members:

Dr. Salomon Amar is a periodontist and is Professor at the Department of Periodontology and Oral Biology of Boston University, Boston, Massachusetts.

Dr. David L. Cochran i s a periodontist and is Chair of the Department of Periodontics at the Health Science Center at the University of Texas, San Antonio, Texas.

Ms. Elizabeth Howe is a consumer representative and is the Outreach Coordinator for the National Foundation for Ectodermal Dysplasias in Auburn, Washington.

Ms. Allison F. Lawton is our drug industry representative and is Senior Vice President for Genzyme Corporation, Cambridge, Massachusetts.

Dr. William J. O'Brien is a materials engineer and is Professor at the School of Dentistry at the University of Michigan, Ann Arbor, Michigan.

Mr. Daniel R. Schechter is the Device Industry Representative and is General Counsel for

Parkell, Inc., Farmingdale, New York.

Dr. Domenick T. Zero is a cariologist and is Chairman of the Department of Preventative and Community Dentistry at Indiana University, Indianapolis, Indiana.

And Dr. John R. Zuniga is an oral surgeon and is Professor at the School of Dentistry of the University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. Dr. Zungia is recovering from an automobile accident and we're pleased he could be with us today.

Joining the Panel members if the following consultant: Dr. Inder J. Sharma is a biostatistics consultant and is an Associate Professor at the Department of Community Health and Preventative Medicine of Morehouse School of Medicine, Atlanta, Georgia.

Joining us at the table is Dr. Susan Runner, Deputy Director of FDA's Division of Anesthesiology, Infection Control, General Hospital, and Dental Devices.

I will now read into the record a

memorandum from the Center Director regarding voting status of our Panel Consultant.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27, 1990 and as amended on April 20, 1995, I appoint the following consultant as a voting members of the Dental Products Panel for the meeting to be held on Tuesday, July 13, 2004. Inder J. Sharma, PhD

For the record, this individual is a special government employee and is a consultant to this Panel under the Medical Advisory Committee. He has undergone customary conflict of interest review and he has reviewed the material to be considered for the meeting. Signed Daniel G. Schultz, MD, Acting Director Center for Devises and Radiological Health, July 8, 2004.

Next I'll read into the record a conflict of interest statement for the this meeting.

The following announcement addresses conflict of interest issues associated with this meeting and is to be a part of the record to preclude even the appearance of impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the Committee participants. The conflict of interest statutes prohibits special government employees from participating in matters that could affect their or their employer's financial interests. The Agency has determined, however, that participation of certain members and consultants, the need for whose services that waives the potential of conflict of interest involved is in the best interest of the government.

Therefore, waivers have been granted for Drs. Cochran, O'Brien and Sharma for their interests in firms that could potentially effect the panel's recommendations.

Dr. Cochran's waiver involves a grant to his institution for the sponsor study for which he had no knowledge of the funding and had no involvement in the data generation or analysis.

Dr. Cochran's waiver is limited in that it allows him to participate in the panel discussion but excludes him from voting.

Dr. O'Brien's waiver involves a grant to his institution for the sponsor;s study for which he had no knowledge of the funding and no involvement in the data generation or analysis. Dr. O'Brien's waiver is limited in that it allows him to participate in the panel discussion but excludes him from voting.

Dr. Inder Sharma's waiver involves a philanthropic contribution from the firm at issue at his institution for which he has no involvement and is uncompensated.

Dr. Sharma's waiver allows him to participate fully in today's deliberation. Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record, the Agency took into consideration on other matters regarding Dr. Domenick Zero. This panelist reported past and current interest involving firms at issue, but are matters that are not related to today's agenda. The Agency has determined, therefore, that

this panelist may participate fully in all discussions.

In event that the discussions involve any other products or firms not already on the agenda for which a FDA participant has had financial interests, the participant should excuse him or herself from such involvement and exclusion should be noted for the record.

With respect to all participants we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement of any firm whose products they may wish to comment on.

I'd like to request that everyone in attendance at this meeting take the time to sign the attendance sheet available at the front door.

Now transmitting you back to Chairman Suzuki.

CHAIRMAN SUZUKI: Okay. Thank you. I note for the record that voting members resent constitute a quorum as required by 21 CFR Part 14.

We will now proceed the first of two open

public hearing sessions for this meeting. The second open public session will follow the panel discussion this afternoon. At these times public attendees are given an opportunity to address the panel to present data or views relevant to the panel's activities. No individual has given advance notice of wishing to address this panel. If there's anyone now wishing to address the panel, because identify yourselves at this time. Okay. Thank you.

I'd like to remind public observers at this meeting that while a portion of this meeting is open to the public observation, public attendees may not participate except at the specific request of the Chair. You will be given no more than 10 minutes for your presentation.

I would like to ask at this time that persons addressing the panel come forward to the microphone and speak clearing, as the transcriptist is dependent on this as a means for providing an articulate transcription of the proceedings of this meeting.

If you have a hard copy of your talk

available, please provide it to the Executive Secretary for use by the transcriptist to help provide an accurate recording of these proceedings.

We're also requesting that all persons making statements during the open public hearings disclose if they have financial interests with the sponsor of the products under consideration.

Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest in the product under consideration, including who is paying for your attendance at this meeting.

Okay. At this time we'll follow the agenda and we will present with the sponsor presentation on the product GEM 21S. Mr. Mark Citron.

MR. CITRON: Good morning. My name is Mark Citron. I'm Vice President of Regulatory Affairs at BioMimetic Pharmaceuticals.

On behalf of BioMinetics we would like to thank the panel and the FDA for the time and

attention that the FDA and the panel have spent in reviewing our PMA and meeting today to provide your recommendation regarding approval of our device.

We have the privilege today to present to you the results of decades of what began as scientific research, progressed to product development and clinical trials leading to today's presentation of the GEM 21S control comparison randomized study results. For the next 60 minutes we will present these preclinical and clinical results and respond to any questions you may have.

I will begin by introducing today's speakers and our agenda.

First, Dr. Samuel Lynch, President and CEO of BioMinetic will provide the brief overview of the GEM 21S device and the development of the device. Dr. Lynch is a periodontist and has conducted extensive scientific research on PDGF as well as other growth factors involved in tissue repair covering many years.

Next, Dr. William Giannoble of the University of Michigan will speak on the mode of

action of GEM 21S with particular emphasis on the growth factor component recombinant human platelet-derived growth factor.

Dr. Ron Nevins, a clinical professor at the Harvard School of Dental Medicine, who is also in private practice, will present the animal and human histology data.

Dr. Bob Genco, who is currently the Distinguished Professor of Oral Biology and Microbiology at the State University of New York at Buffalo and recently appointed the Vice President of Research at the State University of New York at Buffalo will present the results of the randomized control clinical trial.

Finally, Dr. Lynch will provide concluding remarks to the formal presentations.

We welcome the panel's questions, and we have available today several of the key scientific researchers who have been involved in the GEM 21S program, and they are prepared to respond to your questions. These include the study statistician Dr. Phil Lavin. He's an Associate Professor of

Biostatistics at Harvard Medical School and President of Averion, which is a biostatistics consulting firm.

We have Dr. Charles Hart, our Vice President and Chief Scientific Officer.

Dr. Jeffrey Hollinger, the Director of the Carnegie Mellon University's Bone and Tissue Engineering Center.

Dr. Michael Reddy, a clinical professor at the University of Alabama, Birmingham.

And finally Dr. Mark Reynolds from the University of Maryland Dental School.

Dr. Lynch will now begin.

DR. LYNCH: Thank you, Mark. And good morning to the panelists, members of the audience and the FDA.

I would also like to thank the panel for your time and consideration today as well as the FDA for their support and recommendations during the development of GEM 21S.

I believe it is important to note that our meeting today is the culmination of over 15 years of scientific research by multiple investigational

groups working independently and sometimes collaborative. We are fortunate to have many of these research groups represented here today.

Two persons who are not here this morning but who deserve substantial credit for the development of the GEM 21 product, and who I would like to take this opportunity to acknowledge and thank, are Dr. Ray Williams, Chairman of Periodontology at the University of North Carolina and formally Chairman of Periodontics at Harvard. My mentor, counselor and friend.

And posthumously, Professor Harry Antaniales, whose lab conducted much of the early research on PDGF, who inspired much more of the scientific work in this field and in whose lab I trained.

Finally, I would wish to acknowledge my appreciation to the Biomedics Clinical and Regulatory team for their hours of preparing the PMA submission before you today as well as the entire GEM 21 group of clinical investigators who rigorously conducted the pivotal clinical study from both academic

research centers and private clinical practices thereby providing us robust data from both important clinical environments.

We are fortunate today to have three individuals who are involved in the pivotal clinical trial and who are widely recognized for their expertise in clinical and basic scientific research to speak in favor of the approval of GEM 21.

Our first speaker today is Dr. William Giannoble of the University of Michigan and Director of the Michigan Center for Oral Health Research. Dr. Giannoble was a clinical investigator in the GEM 21 pivotal clinical trial, and is a recognized expert on the biology of growth factors including platelet-derived growth factor or PDGF.

As Mark mentioned, Dr. Giannoble will discuss the mode of action of GEM 21S with particular emphasis on the protein growth factor component.

Next Dr. Ron Nevins, a former President of the American Academy of Periodontology and currently the editor and chief of the *International Journal of Periodontics and Restorative Dentistry* who

also finds time for a busy private practice will present will present the animal and human histology data demonstrating the effectiveness of GEM 21 in promoting periodontal regeneration including new cementum and periodontal ligament coronal to the original apical extent of calculus.

Dr. Nevins is uniquely qualified for this presentation, having participated in a GEM 21S pivotal trial also as well as having been the lead investigator for many studies evaluating the human histological response to a number of different drafting materials including PDGF and periodontal bone defects.

And finally, Dr. Bob Genco, past President of the International Association of Dental Research and editor and chief of the *Journal of Periodontology* will present the results of our randomized control double blinded prospective multi-center pivotal clinical trial.

Dr. Genco was the independent medical director for the overall GEM 21S clinical program and has many years of experience in designing, conducting

and evaluating the scientific integrity of clinical trials related to periodontology including having served as the formal of this august FDA Advisory Panel.

Let me now set the stage for these speakers by briefly describing the GEM 21 product, it's development history and the unmet clinical need that it is designed to satisfy.

Next.

GEM 21S, as we have alluded to, principally consists of two main components. One component is a particulate beta-tricalcium phosphate or Beta-TCP, which is filled into a cup and terminally sterilized.

The other principal component is a physiologic solution containing recombinant platelet-derived growth factor, which is aseptically-filled into a syringe just to facilitate handling of the material.

At the time of the surgical procedure, the surgeon or surgical assistant simply peels back the lid of the cup, adds the growth factor solution

to fully wet the graft particles. After a few minutes sitting on the surgical tray, specifically we're recommending approximately 10 minutes, the material then forms a cohesive mass of particles which are then packed into the alveolar bone defect.

Next, please.

One of the main and principle attributes that we would like to stress today is the extensive scientific research known about both principal components of this product, both the PDGF and the Beta-TCP.

There are well over 200 publications on PDGF that deal specifically with its beneficial effect on wound healing. These studies have been conducted in a variety of models and systems including in vitro self-culture systems using primary cultures of osteoblast or well qualified osteoblast like cellnoids, primary cultures of periodontal ligament cells and gingival fibroblast cells and many, many other cell types.

All of these studies in vitro have clearly demonstrated the receptor binding of the BDGT

to the receptors, as you will hear from Dr. Giannoble.

In addition, there are multiple publications showing the beneficial effect of PDGF on a wound healing in vivo in mice, rats, rabbits, canines, swine, nonhuman primates and human clinical trials. As you can see, it's a very well studied molecule.

In addition, PDGF was the first recombinant human growth factor to be FDA approved as a wound healing agent. It is currently marketed under the trade name Regranex by Johnson & Johnson. Has been on the market for over 5 years and is absolutely well documented safety record with no elicitation of antibodies or any adverse responses in commercial use.

In addition, the beta-tricalcium phosphate has is an FDA cleared bone augmentation device. It is the Beta-TCP that we incorporate into GEM 21S. Is on the market in a larger particle form under the trade name Vitoss by Orthovita for orthopedic bone regeneration procedures.

Next please.

Thus, as you will hear this morning the benefits of GEM 21S are it is a fully synthetic bone regeneration system supported by hears of research that have elucidated its mechanism of action and demonstration a strong safety profile. And again, rigorously conducted clinical trials and commercial use.

The PDGT component has specifically been shown to enhance periodontal regeneration in both animals and humans. Our pivotal clinical trial has demonstrated that the product accelerates the attachment level gain and enhances or improves significantly radiographic evidence for bone regeneration.

Finally, we hope to show today that this product demonstrates minimal risk and has the potential for strong benefits in clinical practice.

Thank you very much. And I would now like to turn the presentation over to Dr. William Giannobble to discuss the biology mechanism of action and highlights of some preclinical data on the

product. Thank you.

DR. GIANNOBLE: Thank you, Dr. Lynch.

And I'd also like to thank the FDA and the FDA panel members for the opportunity for me to present to you this morning some of the basic biology in the extent of preclinical data that have demonstrated some of the safety and effectiveness of platelet-derived growth factor the GEM 21S system for the promotion of periodontal regeneration.

So as we look at periodontal disease, which typically it's a disease that results from a microbial infection that leads to the resorption of alveolar bone through to its cementum and periodontal ligament. There are a variety of different factors that appear to be critically important to the reconstruction of periodontal wounds; those being the appropriate cells within the lesion, they can repopulate the wounds such as osteoblast, cemental blasts, periodontal ligament fibroblasts within the presence of the appropriate scaffold that will then allow cell ingrowth and vascular invasion into the lesion.

And then the usage of signaling molecules or growth factors that can direct the migration of cells into the wounds, promote proliferation of the cell types within the defect and stimulate matrix biosyntheses.

In addition, given that the structure is a vascular, it is critical to provide an angiogenic environment to promote new blood vessel formation to reconstruct these periodontal wounds. And so in my presentation this morning I will focus on platelet-derived growth factor and the scaffold, the osteoconductive scaffold beta-tricalcium phosphate for use in promoting periodontal regeneration.

So as we look at the two key components of the GEM 21S system, the first being the Beta-TCP, as this is an osteoconductive scaffold that promotes cell attachment ingrowth, it also has been demonstrated to prevent soft tissue collapse into the soft tissue defects, and also facilitates blood clot stabilization during the initial wound repair process.

Recombinant human platelet-derived growth

factor BB there is a very extensive profile in terms of its demonstrated ability to promote chemotaxis of the key cell types involved in tissue repair. It is also mitogenetic or promotes proliferation of these various cell types such as periodontal ligament fiberblast and osteoblast.

And PDGF has also been demonstrated to be to be an angiogenic molecule by recruiting smooth muscle cells that are important in the formation of new blood vessels.

Next slide.

So to go into a bit more depth on beta-tricalcium phosphate, this is a synthetic purified calcium phosphate ceramic that has a very extensive history in the FDA as well as a device used in dentistry and in orthopedic applications as a bone void filler. And in this long history of usage there have been no demonstrated adverse events utilizing beta-tricalcium phosphate as a bone void filler in these varieties of applications. And recently the FDA Advisory Panel recommended a reclassification of Beta-TCP from a high risk device to a lower risk

device for use in dental applications.

This slide demonstrates scanning electron microscopic views of beta-tricalcium phosphate at lower power magnification here and a higher power magnification. The low power view demonstrates the beta-tricalcium phosphate granules which in the formulation for the GEM 21S system range in particle size from 250 to 1,000 microns in diameter. This higher magnification view demonstrates the very open pore structure of the Beta-TCP used in the GEM 21S. It has a 90 percent open pore structure which then this porosity, this ranging from 1 to 1,0000 microns in diameter thus allows cellular ingrowth and vascular invasion. This lower panel demonstrates at a different microscopic view the growth of osteoblast like cells on top of the beta-tricalcium phosphate demonstrating that it does promote cell attachment and proliferation on the device.

Recombinant human platelet-derived growth factor has been an extensively studied molecule in the area of wound healing. So it's a natural wound healing hormone released from platelets during normal

wound repair.

The scientific established mode of action is that PDGF has been demonstrated to promote connective tissue formation, also osteogeneses and angiogeneses by the induction of vascular endothelia growth factor in the recruitment of smooth muscle cells.

This diagram depicts the binding of platelet-derived growth factor, which is a dynaric protein which binds to cell surface associated tyrosine kinase receptors. These receptors dimerize and then elicit autophosphorylation of the receptor. This autophosphorylation event then leads to a variety of different signal transduction pathways which will then led to the elicitation of the variety of different biological effects such a mitogenesis or cellular proliferation, directed cell mitigation or chemotaxis, and also the blocking of program cell death or promoting cell survival.

So PDGF more specifically as we examine its ability to promote periodontal regeneration within the periodontia, platelet-derived growth

factor and its associated receptors are naturally induced during normal tissue repair, both soft tissue repair and during the fracture healing procedure.

PDGF has been demonstrated to be chemotactic for a variety of cells derived from the periodontia as well as promoting cellular proliferation and matrix biosynthesis. And there is a large body of work supporting the variety of effects as shown here.

PDGF also promotes cell survival since a PDGF alpha receptor encodes for a growth arrest specific gene. So PDGF will promote or prevent apoptosis or programmed cell death.

PDGF also enhances angiogenesis specifically by promoting the proliferation of smooth muscle cells or parasites around the newly formed blood vessels and it compliments the actions of VEGF or vascular endothelia growth factor that's critically important for blood vessel formation and maturation.

This slide published by the San Antonio group demonstrates the effects of recombinant human

PDGF in an artificial wound model on promoting cell repopulation. And so what we can see in this slide looking at percent wound fill or cell repopulation of periodontal ligament fiberblast versus a low serum control, this graphic demonstrates that over a period of ten days the significant increase in cellular repopulation into artificial wound defects by the application of recombinant human platelet-derived growth factor.

Next slide.

This slide demonstrates the ability of platelet-derived growth factor applied onto the beta-tricalcium phosphate osteoconductive device for its release and then subsequent biological activity of the release PDGF. And so this slide shows treated Thymidine incorporation as a method to determine DNA synthesis over time when PDGF has been applied to the beta-tricalcium phosphate device. And so what one can note is that there is a rapid release over the first 24 hours and the PDGF that is released is indeed biologically active as measured of the promotion of DNA synthesis.

This slide demonstrates results from an in vivo animal study done in Beagle dogs where fenestration bony defects were created on two surfaces and then autoradiography was performed to look at cells that were demonstrating active proliferation within the periodontal wound compartment.

So the variety of different cell types examined were those important in periodontal repair such as fibroblasts, cementoblasts, osteoblasts, perivascular and endothelial cells. And what was noted that it was compared to control or surgery alone defects, PDGF promoted at least a three to five full increase in cellular DNA synthesis as noted by the autoradiography. And you can see this in a multitude of different cell types that were found within the lesions, thus demonstrating that the PDGF has pleiotropic effects on promoting a variety of parameters associated with periodontal regeneration.

This slide published by Bob Genco's group several years ago in a canine model of surgically created critical size defects in dogs. These are

class 3 furcation defects that do not typically heal.

The defects were treated with guided tissue regeneration, a standard treatment modality for periodontal regeneration versus recombinant human platelet-derived growth factor applied to the tooth root surface combined with GTR. And looking at histomorphen metric analysis to determine the amount of regeneration that occurred within the defects, what was noted was that PDGT strongly augmented the degree of newly formed bone and periodontal ligament, while at the same time blocking really the production of the granulation tissue or scar formation that resulted after this healing period.

This slide demonstrates the potent effects of platelet-derived growth factor on promoting osteogenesis. This is a study published several years ago that examined an osteoporosis model where female rats were ovariectomized which induced a rapid bone loss. And the slides on the left demonstrate the metathesis of the tibia in these animals either in an osteoporosis saline control or animals that were delivered a three times per week

infusion of 2 milligrams of recombinant human platelet-derived growth factor.

What one can note from these long bones was that there was a significant increase in the boning trabecular in both the primary and secondary spongiosa in these bones that were treated with -- these animals that were treated with recombinant human PDGF.

Using histomorphic metric analysis of the vertebral body and then tibial metathesis once could also note a statistically significant improvement in bone density measures nearly two-fold in both of these different bony sites.

This slide now demonstrates the platelet-derived growth factor's ability to promote periodontal regeneration. This is a natural disease model in the Beagle dog that will result in loss of connective tissue and alveolar bone. So this slide demonstrates a through and through class 3 furcation defect that typically will not heal on its own. These animals were delivered a single application of recombinant human platelet-derived growth factor in a

beta-tricalcium phosphate carrier, and this slide shows six weeks after this single application of PDGF plus the Beta-TCP. The promotion of new alveolar bone, a periodontal ligament and tissue consistent with cementum.

These various preclinical animal studies performed in dogs were also followed by in nonhuman primates in the monkey model Macaca Fascicularis. And what this side is demonstrating is the consistency of effects in the animal model Macaca Fascicularis versus humans when platelet-derived growth factor was combined with insulin like growth factor one. So this study looked at animals that were treated with a single application. If you look at the parameter of ostis defect fill, there is a striking similarity between the monkey model and this is -- the human data here is derived from a multi-center trial done, it was a phase 1 phase 2 trial done at the Harvard School of Dental Medicine and at the University of North Carolina. And essentially the bottom line of this study was demonstrating that similarity between the animal model and the human.

Next slide.

The next few slides will now demonstrate the extensive track record for the various components used for the GEM 21S product. And with the Regranex product that has been FDA approved for, it's been over five years now, it has a very extensive safety record. And so the results shown here are actually a compilation of six randomized controlled trials where the Regranex product demonstrated extensive safety. There was no neutralizing antibodies that were developed. And these patients received the treatment of the Regranex every other day for up to 140 days of a concentration of 100 milligrams per mil of the PDGF. And so to date there have been at least 17 million doses applied of Regranex, demonstrating its safety.

Also you have provided to you very extensive confirmatory biocompatibility tests. As you can see on the list here, in terms of cytotoxicity, sensitization, acute systemic toxicity, genotoxicity and muscle implantation for the GEM 21S product. And so all of these tests have demonstrated

that GEM 21S is both biocompatible and safe.

So what I would like to summarize for you this morning is that we have demonstrated that the mechanism of action of platelet-derived growth factor is well established as shown in vitro studies as well as in vivo applications demonstrating its potent ability to promote periodontal regeneration, i.e., tooth group cementum, periodontal ligament and alveolar bone.

This is also a very long history of safety for both of the components, the beta-tricalcium phosphate in both dental and orthopedic applications and the platelet-derived growth factor component, i.e, in the Regranex product for the treatment of neuropathic diabetic ulcers.

The results have also been demonstrated to be quite consistent amongst the large body of research done with a variety of different clinical investigator reclinically that bridge and demonstrate consistency to some of the human clinical studies that have been performed.

I would like to thank you for your

attention and I look forward to the discussion this afternoon.

I will now introduce Dr. Myron Nevins who will present the proof of principle data on the ability of platelet-derived growth factor to promote periodontal regeneration in humans.

DR. NEVINS: Good morning.

I'd like to take this opportunity to thank the FDA and the panel by allowing us to demonstrate the evidence of regeneration, periodontal regeneration that we've been able to achieve with GEM 21S.

The definition of periodontal regeneration is histologic. It has evolved from proceedings of two world workshops in clinical periodontics and it is inclusive of information of new bone, new cementum connected by a functional periodontal ligament on a root surface that has previously been pathologically exposed.

The hierarchy of evidence in periodontal regeneration has taken years to evolve, but because of the histologic definition, it's clear that the

most compelling evidence are human studies that have histologic evaluation. In lieu of the obvious difficulties in obtaining this information, other means have surfaced to measure success, including RCTs with measuring clinical invaded ethic parameters. Perhaps the more contemporary benchmark has been the use of, be it surgical reopening, which would more closely mimic the radiographs in terms of interpretation.

Proven principle assessment is established to demonstrate the safety and the effectiveness of a product. Safety would determine histologic tissue reactions, healing response and provide a clinical assessment for safety. Effectiveness provides human histologic evidence of regeneration, in this case for vertical intrabony defects and also for Class II furcation invasion problems.

This design include 11 intra-osseous defects around teeth scheduled for extraction, six intrabony and five Class I furcation defects were treated. They were treated with a combination of

recombinant BDGF plus a carrier. At nine month post-operative follow-up recordings of the CAL, the pocket depth gingival recession and linear bone -- were recorded. At that time the teeth were abstracted with a small amount of surrounding tissues and submitted to blind histologic analysis to assess regeneration.

I should mention at this moment that informed consent was obtained from the patients. The patients were rehabilitated from the site with bone crafting, dental implants and a prothesis to reestablish or in all senses to provide them with a dental solution that they would not have been able to have otherwise.

The intrabony defect results demonstrate a pocket depth, a mean pocket depth of 9.7 millimeters and at nine months at time of the harvesting block, 3.3 millimeters. This is a change from baseline of 6.42.

The importance of this is related to length of roots in a human model. The smallest, the shortest roots are the incisors, the central incisors

with 11 millimeters and of course the longest would be the cuspids which approximate 18 millimeters.

If we accomplish a 6 millimeter correction, this definitely changes the prognoses of the tooth.

The CAL gain started -- level started at 11.1 baseline and was 4.9 at nine months. Once again, for a change from baseline of 6.7, which is consistent with the pocket depth reduction.

Bone height change shows radiographically a 2.14 improvement.

This will become in a few minutes when we look at the histologic measurements, because there will be a correlation between what was here radiographically and histologically.

The furcation defects from a pocket depth began at 6.2, in nine months were 2.8 for a change from baseline of 3.4. And the clinical attachment level changed with a change from a baseline of 4.

Since these were horizontal as well as vertical probing depths, these are very significant in reversing the invasion of the furcation by

inflammatory periodontal disease.

When the teeth are described as being candidates for extraction, it's most effective when we look at a clinical photograph. And here we see a maxillary cuspid with bone defects both in vertical dimension and bone morphology that would be serious candidates for extraction.

We determine the level of the root that has been exposed to disease by the presence of calculus. So at the base of the calculus a notch is made with a small burr to designate that we actually have evidence that disease occurred at that point.

The calculus, of course, is removed before we continue on to place the crafting material.

Next.

After nine months when the block was removed or harvested, we now have an opportunity to witness the histology in evidence.

Here we see a lower power and we're going to observe three different situations. One, the area of the notch where we can see new cementum, new bone and a new mature well vascularized periodontal

ligament. If you look closely, you can see sparky fiber attachments on both the bone and the cementum side. So the area of the notch which was placed at the base of the calculus has responded appropriately.

Now, in the next observation we'll look at mid-root and then we'll look at the mouth of the defect.

As we move occlusally we again witness new bone, new periodontal ligament and a functional vascular periodontal ligament with clear evidence of sparky fiber attachments on both sides indicating its function.

Coming to the mouth of the defect, the new cementum has come all the way to the beginning of the bone defect and we have new bone and, once again, the functional periodontal ligament with supercrestal fibers that show very little evidence of any inflammatory infiltrate.

This completes the picture of that cuspid that we witnessed.

Looking at a second vertical defect just to demonstrate quickly that this occurred more than

one time, we again observe a notch. We see in the notch new cementum, new bone connected by a functional vascular periodontal ligament, and in fact we have new cementum and new bone all the way to the top of the defect.

We have studied several different materials, but this astounding to see complete regeneration of the defect.

Next.

However, the most exciting observation that we encountered was the response in Class II furcations where there has been evidence to suggest that we fulfil the definition of periodontal regeneration with any of the materials that are presently available.

The notch designated the extent of the calculus and if we take the excerpt from the box, we see new cementum and new bone connected by a new functional periodontal ligament, again with evidence of sparky fiber attachments and no evidence of epithelium.

The outstanding observation in my

estimation is that even at the fungus of the furcation there is no evidence of epithelium and we've completely resolved the definition of periodontal regeneration with new cementum, new bone and new periodontal ligament. This offers us the opportunity clinically to provide resolution for a problem that escaped clinicians indefinitely.

Next.

The results and conclusions of this human histologic evidence demonstrate safety; there's normal bone and ligament remodeling. The clinical measurements were demonstrated to be significantly improved. Radiographs were consistent with bone fill. We have no evidence of root resorption or ankylosis.

Actually, the histo micromophy that was performed very closely related in size or dimension to the radiographic analysis that was performed.

There is no evidence of root resorption or ankylosis whatsoever, so there is nothing to discuss along those lines. And the histologic evaluation we just saw revealed regeneration in both

the intrabony and Class II furcation defects.

It became time to design a pivotal study. And in doing so, the transition was made to GEM 21S. There were two issues: One, select a carrier and the other to give some consideration to dosing.

Allograph was used for the histologic study. Since it's not formally approved by the FDA, a lot of questions -- a lot of producability remained and consideration was given to trying alternatives. Since beta-tricalcium phosphate and allograft were shown to provide comparable delivery properties of recombinant PDGF. The kinetics are similar and the BDGF release from both matrices simulated bone cell proliferation.

The study objectives were to compare the in vivo performance of PDGF with the two carriers, beta-tricalcium phosphate and allograft.

It was also to access the dose response of the recombinant PDGF.

The study designed is a randomized control blind trial and in canine this critical size periodontal defects. Six defects were made in each

group and there is an eight week follow-up.

Looking at the results we can see that the beta-tricalcium phosphate by itself demonstrated new bone formation, but particles of the carrier remained and obviously it has left a significant portion of the furcation without periodontal regeneration. However, when the product GEM 21S is used the combination of the recombinant PDGF with the beta-tricalcium phosphate received a notch and received complete regeneration with cementum and periodontal ligament indicating a much more favorable response in the type of clinical end point goal that we would hope to achieve for our patients.

Next.

Evaluating the results of the canine study we see results with both TCP and allograft. And it's clear that the dosage of .3 mg/ml with the TCP and PDGF outperformed the other possibilities.

Next.

This led to the overall conclusions that GEM 21S, a truly synthetic system is safe and biocompatible with no risk of disease transmission.

The BDGF when used with beta-tricalcium phosphate or allograft significantly improved the periodontal condition. This is measured in the formation of new bone, new cementum connected by a functional periodontal ligament.

There was sufficient evidence to now initiate a pivotal clinical trial and the decision was made to use the .3 mg/ml of BDGF because of the greater effectiveness that was shown.

And now I have the pleasure of introducing Dr. Robert Genco, the Director of the Periodontal Disease Clinical Research Center at the State University of New York in Buffalo. Bob has carried out five phase three and pivotal trials of periodontal products that have previously been accepted the FDA, so he's an old hand at it.

DR. GENCO: Thank you, Dr. Nivens.

And I, too, would like to thank the panel for your special efforts in reading that mass of material that was submitted to you. I have the file; files and files of those submissions and I know what a tremendous effort it is.

I would like to also thank the FDA, as Sam did, for their help during the design and analyses of the pivotal trial.

Now, I've worked in this area for about 15 years. One of the groups that Sam mentioned was the Buffalo group that looked at BDGF and other growth factors, and I have a tremendous interest in seeing this come to the benefit of society. And I'm very pleased to present this material today.

I have an official role with the company. I'm the Chairman of their Scientific Advisory Board. And longstanding interaction with Dr. Lynch.

I'd like to talk about the pivotal trial and share some of the results with you, the highlights the results. The next slide shows the nature of the trial. It was a double -- prospective randomized control trial with 180 patients randomized to three treatment groups.

Group one was Beta-TCP plus 0.3 milligrams per mil of recombinant PDGF beta subunit.

Group two TCP plus 1 milligram per mil of recombinant PDGF.

And then group three is interesting in that it's an active control. It's TCP with buffer, no recombinant PDGF. And it's an active control in that it's a product that's already on the market for bone regeneration used in orthopedics extensively. And we used a super fine fraction of that Vitoss. And it's a newly formulated form with increase porosity and increased surface area. And really it hadn't been systematically tested in periodontal disease. So, the design is really -- puts a high hurtle to show an adjunctive or additional affect of recombinant BDGF, and you'll see some of the results that bare that out.

It's a six month follow-up study. And we looked both at clinical and radiographic pinpoints.

The study was carried out in 11 centers, four university centers and 7 private clinical offices.

Next slide, please.

The investigators, patients, sponsor and monitors and radiographic assessment was all masked. The patients were randomized to one of the three

groups by a variable block design, and all of the investigators; that is the examiners who were separate from the operators, separate from the surgeons, the examiners were calibrated, both at baseline and at six months to ensure inter and intra examiner standardization.

Next slide, please.

The study was independently monitored for quality and safety performed by Target Health, and it was independently analyzed by both Target Health and Averion, Dr. Phil Lavin's company, and he's here.

Next slide please.

The key inclusion criteria were:

Age, 25 to 75 years; the pocket depth of the treatment site had to be at least 7 millimeters deep and had to have an intrabony defect at the time of surgery of at least 4 millimeters.

Any configuration of pocket was allowed. It could be 1, 2, 3 combination, combination with circumferential and combination with Class I or II furcation. So these are real live complicated complex intrabony lesions.

We allowed smokers who smoked up to one pack per day. The rational was that many, many patients who suffer periodontal disease are smokers. So we wanted to make sure that this was a treatment that would work in smokers who are known to heal less well than nonsmokers.

Next slide.

The key exclusion criteria included pregnant women or women intending to become pregnant during the study. This was not excluding women of childbearing age. Only those that were pregnant, lactating or intending to become pregnant.

History of oral cancer or HIV. Signs of acute infection or abscess at the site, the test site, Class III furcations, surgery under study too from the last year; all of these were exclusion criteria.

Next slide, please.

The outcome measures are very important to comment to. Clinical attachment level was assessed both at three months and at six months. Linear bone growth and percent of bone fill are

quantitative measurements of radiographs. These were assessed as companion outcomes. And as we have heard from the previous presentations, in this complex disease, periodontal disease, the pathology involves both soft tissue and hard tissue, so it's reasonable from the clinical pathologic standpoint to assess both tissues, hard and soft for clinical outcome.

Then we also used a composite outcome where we blended or we merged, melded both the clinical and the radiographic technique. And the rationale for that is to get at this question of clinical significance. To try to address the issue of what percent of the target population benefitted from therapy. It wasn't meant to look at statistical significance to prove the efficacy. It was to get at this very difficult question. I know I was on the panel for a number of years. We always wrestled with the question of is significant. Did it benefit a significant portion of the target population? And that's why we used this composite outcome.

We also looked the pocket depth reduction, gingival recession and wound healing. And

at the direction or suggestion of the FDA we compared it to currently approved FDA therapies that were sort of comparable.

Next slide.

This is the study time table. I draw you attention to day zero to the day the surgery was carried out. At least or less than two weeks prior to that baseline examination, examiner calibration and radiographs had to be made. At least two months prior to that the patients had to be screened, informed consent obtained and an initial preparation carried out.

After surgery the patients were followed at three months and at six months, radiographs were taken and all of the clinical measurements made both at three and six months.

The next is a videoclip of the actual preparation of the material. And this shows the dry material in a dappen dish and the PDGF solution added to it from the sterile syringe. And then the material is next. And this is done approximately ten minutes, at least ten minutes before the material is

applied. You can see how the particles adhere to each other, and it's actually a very easily managed material to place in the mouth when you're having to place the material in upper lesions or mandibular lesions. It's actually quite easy to work with.

The next is a videoclip of the actual surgical procedure. And this is from one of the clinical sites. You can see the initial probing was carried out. And the -- we'll get some -- there we go. The videoclip shows the depth of the pocket. You see the tissue is quite firm after the initial preparation.

Then the root is thoroughly debrided. The issue is removed. All the granulation tissue is removed from the lesion. The lesion, you can see the dimensions here. It's a 3 wall intrabony defect. The root is cleaned absolutely clean. And then the root is treated with tetracycline to condition it. And then material is placed in the lesion to fill the lesion to the brim. And it's packed gently into the region.

You can see how easy it is to handle.

The operators, the surgeons were all standardized. They were standardized to a standard way of making an incision, incision design, to a standard debridement of the root, to a standard use of tetracycline concentration, duration.

And as you can see here, see the incision is a scalloped incision and we standardized the suture technique so that the buckle flaps could be opposed to get primary tension healing. Very, very important in these regenerative techniques to make sure that we get full coverage inasmuch as possible of the lesion with the soft tissue.

Now the examiners, as I mentioned, they were different than the surgeons. Different set of people. They were calibrated. They were calibrated to look for reproduceability of their own measurements, and that's inter-examiner calibration. And they were calibrated against a gold standard. Someone on the research team who had an intrinsic low error, all of the other examiners were calibrated against that person to ensure consistency across sites so we had more confidence to prove the data.

The next slide shows the actual results. The Kappa for the intra-examiner reproducability was 0.94 and for the inter-examiner consistency was .89. Both very, very high levels of reproducability and consistency exhibited by those Kappas.

Now the radiographic analysis. Care was taken in that also. For example, the films were taken under a uniform height quality field conditions using the renperil system, and every investigator's team was standardized to take these x-rays at a high quality uniform way.

Then the films were sent to a central site, University of Alabama, and Dr. Reddy and his team used standardized techniques and validated measurements which they and Dr. Genco for a decade had developed over the years to measure both linea bone growth as well as percent bone fill. And this is really percent linear bone fill. It's not a volume. It's a two dimensional measure.

And I'll show you those measures on the next slide. This is a graphic diagram of the radiograph and the landmarks that were measured at a

synitho enamel junction, or if there is a filling, it would be the apical portion of the filling, restoration, root apex, crust of bone, base of defect at baseline, and similar measurements at six months. And then the next slide shows how these calculations were made.

First, linear bone growth is very simply the measurement from the CEJ to the base of the pocket at baseline, and subtracted from that is the measurement from CEJ at the base of the pocket six months later. Now in this instance, it turned out to be the original value of 6 millimeters, and at six months 3 millimeters, so we have three millimeters of linear bone growth. It's that simple, but very precisely measured.

Now percent bone fill-in is simply the linear bone growth divided by the initial depth of the lesion. In this instance, it would be 50 percent, so the original depth of the lesion is 6 millimeters and the linear bone growth was 3, so you had a 50 percent bone fill. It's a linear bone fill.

Now as a matter, because these are field

x-rays, they're not taken with stents or any other precaution except good technique. There was a control on elongation or foreshortening, and that was the measurement of the CEJ to the apex, and that was measured on all x-rays pre and post. If they varied by 15 percent either way, then the x-rays were adjusted. They were normalized, a very standard technique used in radiographic analysis. We've used it for years and it works quite well. Now in fact that happened in less than 5 percent of the cases which test to the quality of the x-rays site by site. Next slide, please.

Now once the x-rays are sent to the site, then there's a whole other set of calibrations and measurement variability assessed; that is, the actual measurement of the x-rays at the site. The technician made repeated measurements on randomly selected cases, and there was a less than 3 percent variability between measurements, which is very good.

Following assurance, all radiographs were then looked at, reviewed by an independent periodontist. And, of course, all the radiographs

are blinded anyway so nobody in Alabama knew which group they were from, but the independent periodontist who was not connected to the study looked at the x-rays and looked at the measurements to see if they made sense; were there any really odd-ball measurements. And they were occasionally some measurements that didn't -- so those were remeasured, so there was another level of control placed on the measurements. Next slide.

Now the results. I'll first summarize all the results in the next slide, and then go into them individually. First of all, there were no device-related serious adverse effects, an expected result, but it had to be proven. You're using two FDA approved products, put them together, both are safe, together they're safe, but it had to be proven.

GEM-21S significantly improved, that is statistically significantly improved CAL at three months. It significantly improved CAL gained between zero and six months. And the area under the curve assessment showed that the three month gain was maintained, it was a really accelerated healing which

was maintained at six months. The LPG, that's the linear bone growth, was significantly improved at six months, as was the percent bone fill at six months, and these were highly significant in the .001 range. And the GEM-21S exceeded the benchmarks of effectiveness as compared to Emdogain, an FDA approved product, PepGen P-15, an FDA approved product, Allograft which is FDA allowed, not necessarily approved but it's allowed, and open flat debridement. Next slide, please.

DR. SHARMA: Excuse me. I want to just clarify one thing there. These results you're talking about, they are baseline to certain time point.

DR. GENCO: That's right.

DR. SHARMA: Not to compare it with different groups. Right?

DR. GENCO: I'll get into which group, yes. It's the .3 milligram group. That dose group showed these differences, and not the one. Right. But I'll get into that in some detail. I just wanted to give an overview, the result of my judgment and

education; that Aristotle technique of tell them what you're going to say, say it, and tell them what you said. So I just told you what I'm going to say. Now I'm going to say it.

DR. SHARMA: All right.

DR. GENCO: The number of subjects were 180, 178 finished with a 1 percent drop-off rate, which is amazing for such a study. Forty-three smokers, mean age 51, gender slightly more males than females, approximately 60 percent Caucasian, the rest distributed among Asian, African American and Hispanic. Next slide.

Now baseline defect characteristics, the message here - there were no significant differences among treatment groups, and you can see this in the data, this inspect pocket clinical attachment level, bone defect, percent one wall, percent two wall, percent three wall, circumferential. They're all approximately the same, which you'd expect that random variation you get by randomizing. No statistically significant differences. And this is extremely important as we'll see later, because the

deeper the pocket, the more healing you're going to get, so you really must have all the pocket depths at the baseline comparable. Next slide.

Now let's look at total adverse events. No significant differences among the treatment groups with respect to any adverse events, serious, potentially related, unrelated. For example, subjects with at least one adverse event ranged around 70 percent. Well, they all had surgery, and what was that adverse event; pain after surgery, which is to be expected. Not different between the surgical control and the other treatment groups, so there's no effect here of increasing adverse events by adding PDGF to the TCP. Let's look at the serious adverse events. They were present. They were not different among the groups, but they were present. Let's look at them. Next slide.

There were four serious adverse events, none related to the study device; including bronchitis, basal cell carcinoma, spinal fusion surgery, and diabetic complications. These are things as we all know in a six month study with 180

patients, you're going to get these adverse events - not related to the device.

Now let's look at some of the measurement data. One assessment is clinical attachment level gained over three months and over six months comparing the .3 milligram, the 1 milligram and the TCP, and you can see that the .3 milligram was statistically significantly different than the control at three months. That 3.8 millimeter gain was more or less maintained at six months. However, what happened, I think, is that the TCP control gained - and we saw this with the dog study too. The control actually catches up to the treatment over time, so now the difference between .3 milligram and TCP is not statistically significant. And we'll look at this another way looking at the area under the curve analysis. Next slide, please.

Now if we compare the gain of GEM-21 with the CAL gain of Emdogain and PepGen using the three studies for Emdogain that were submitted to the FDA and the two studies for PepGen, using those studies as a baseline, you can see that 3.7 CAL gain versus

2.7 versus 1.7, at least it's comparable, highly unlikely that GEM-21 under-performs, but at least they're comparable. Next slide.

Now one of the problems with such analysis, you have to really be careful as you all know, is that the studies were not done head-to-head. They are separate studies. We're talking about three, two, in our study five different, six different studies compared. And the possibilities for making misinterpretations are great.

For example, if you look at the baseline pocket depth, they're pretty comparable between our study and the Emdogain studies, but look at the PepGen study. They started out with shallower pockets, so the comparison with PepGen is fraught with difficulties, because they started with lower pocket depth so they're going to get less healing. And, in fact, that's what we saw. So we really have to be very careful about the interpretations compared to products on the market, and we are.

So what we say is they're comparable, very unlikely that GEM-21 under-performs relative to

the others, so I think that's a conservative way of stating those comparisons. Next slide, please.

Now the area under the curve is commonly used in wound healing studies, and its purpose is to detect differences in CAL gain among the treatment groups between baseline and six months. We're using data from zero, three, and six months. Next slide, please.

And here are the curves. The green line is the 0.3 milligrams, and you can see it out-performs the other two groups at 3 and at 6. Our interpretation is that this is an early gain over the other two groups, statistically significantly different at .3 milligrams and the control, and then it's maintained. And if you look at the area under the curve, there is a difference between 0.3 milligrams and the other two, which is statistically significant at the 0.54 level. There is one subject here who suffered an abscess during the healing phase who lost four millimeters of attachment. If you remove that attachment that subject just becomes 0.033. However, we didn't remove that subject

because it's an intent to treat analysis. Next slide.

Now let's look at radiographic linear bone growth as the companion. Here the .03 milligram per mil out-performs the 1 milligram per mil, and both out-perform the TCP alone in terms of radiographic bone analysis. And these P-values are very, very strong, even taking into consideration multiple variable comparisons using Yates Correction or other techniques. These P-values are extremely powerful. Next slide, please.

Now if we compare against current therapies again with the caveats I mentioned before, clearly GEM-21 is comparable to Emdogain - 2.5 to 1.1 and probably better than Allograft, certainly better than surgery alone. Next slide, please.

Now let's look at this radiographic percent bone fill. That's this derived ratio of linear bone growth as related to the original pocket depth. And here the mean percent bone fill is on the X-axis, and the three groups are depicted by the bars. Again, the green bar in the 0.3 milligram per

mil out-performs both the 1 milligram per mil, and both out-perform the TCP alone, and the P-values again are quite low, showing high levels of statistical significance. Next slide.

And now comparing radiographic bone fill with the predicate products, you can see that GEM-21 is comparable to and probably performs better than the other products with respect to percent bone fill. But certainly it's comparable too. Next slide, please.

Now if we look now, drill down into the data and look at the various types of lesions we're treating, you know the one and two walls are very difficult to treat as to the more contained three-wall and circumferential. And you can see that in the data. You look at all of these bars for the one and two-wall are lower than all of these bars for the three-wall and circumferential, so in general, these lesions heal better than these; yet, the 0.3 milligram per mil GEM-21 gave 50 percent bone fill in over half the subjects in those very difficult to treat one and two-wall lesions. Again, out-

performing the 1 milligram per mil and out-performing the TCP. And if you look at the three-wall and circumferential defects, 65 percent of the lesions were filled, or the lesions were filled 65 percent of the bone with the 0.3 milligram, as compared to 34 and 21 for the other one control. Again, the .3 milligram out-performs the TCP and even these defects that heal on their own.

DR. SHARMA: Is this all this radiographic data at three months or six?

DR. GENCO: Well, it's at six months. All the radiographic data is at six months. The CAL data is at three and six. Now the reason the radiographic data at three months is not used is because the material is in the lesion at three months. You can see it on the radiograph. And from the histology, which we've done extensive histology both in man and animals, it's usually gone by three months histologically, you can't see it any more. So we felt safe in looking at the six month x-rays. Next slide, please.

Now this is a distribution of the

cumulative proportion of bone fill and the curve to the right, right is better, left is worse. You can see the curve to the left is the control, and if you look at the proportion, let's say 50 percent of the subjects with control, 20 percent bone fill. In other words, in 50 percent of the subjects given the control, you got 20 percent bone fill, not very good. And 33 percent and 50 percent of the subjects given the 1 milligram per mil, they got 33 percent bone fill, but in 50 percent of the subjects with .3 milligram, we got 50 percent fill, so half the subjects, half the pockets were filled with .3 milligram, 20 percent of the subjects or half the subjects, 20 percent fill with the control. Again, statistically significantly different. This starts to address the issue of clinical significance. What proportion of the population actually benefits from this? It's not meant to be the statistical proof for efficacy, but some indication of how many people in the population are actually benefitting from this treatment which addresses clinical significance.

Now the rationale for the composite

outcomes is just as I said, to get some indication of clinical significance. So we use the two primary end-points, CAL and bone, and then made a composite. And this is done in rheumatology and other areas of wound healing. As a matter of fact, we're carrying out a study of cardiovascular disease and we're using a composite of six different cardiovascular variables, so composite variables I think are gaining in attention in the clinical trial methodology area, and are extremely useful when done properly. Next slide.

So how do we define a successful outcome? Well, what we did is we took the PMAs for Emdogain and PepGen and took their best results, and we said all right, that's the attachment gain achieved by either Emdogain or PepGen, and the best bone fill or linear bone growth will accept as the cut-off point. Okay. So we put that together. The best attachment gain for Emdogain or PepGen was 2.7 millimeters, and the best bone fill for either was 14.1, so we put those together. That's our composite. If you reach that, we define that as "success". Same for CAL and

LPG, 2.7 millimeters and 1.1. Let's see what the results are.

Now look at this overall. Success was achieved with .3 milligram dose using one of those composites in 70 percent of the subjects, and with the other composite, it's 60 percent of the subjects. Now did the percent success out-perform the control? Yes, but that's not the intent here. The intent here is not the statistical significance, although it was highly significant, but what percent of the population achieved this definition of success? We're quite pleased that 60 to 70 percent of the population benefitted from this product. Next slide, please.

Now let's look at one of these lesions. This is a lesion that after breaking the code, we know got the .03 milligram per mil, a 44-year old female with a lesion above the two-wall defect which was circled around the lingual with a class two furcation, and you could see the defect on the distal. You could see it here. And if you look now at the six month x-ray, this is new bone. This not

TCP, this is new bone. The TCP is little particles that you could see on the x-ray, very characteristically different than the new bone. So when you make the measurements from the CEJ to the base of the defect, in this instance it's something like 6 millimeters, and in this instance it's something like 3, so we had about a 50 percent fill, just rounded off with a linear bone gain of about 3 millimeters, so this is a typical result of 50 percent fill and 3 millimeter bone gain.

Now as Dr. Nevins mentions, this markedly changes the prognosis of that tooth. The lingual furcation is filled and the distal lesion is pretty much 100 percent healed, and the mesial lesion is about 50 percent healed. This is a very good result clinically. Chances are we've gone from a 6 millimeter, 7 millimeter pocket to a 3 millimeter, 4 millimeter site. That's maintainable. Next slide, please.

So in summary then we had 180 patients who were fully masked in this perspective multi-center trial. Quality was assured by multiple

mechanisms, including CRO, blinded investigators, blinded design, arm's length statistical analysis by CRO and another firm. There were no device-related serious adverse events. The GEM-21 has statistically improved CAL at three months, and the CAL under the curve between zero and six months, and the interpretation is it's rapid healing which persisted at six months that was induced by the .3 milligram per mil growth factor.

The linear bone growth was improved at six months as was the percent bone fill at six months in a highly statistically significant manner. We feel that the GEM-21 exceeded benchmarks of effectiveness but for caution we'll say it was comparable to the benchmarks, very unlikely to be less effective than already existing products on the market. Next slide, please.

Now let's look again at the comparability to the approved products, the GEM-21S, CAL gain 3.7, radiographic fill 2.5 are in the ballpark if not better than the other approved products. Next slide.

So overall then, we feel that GEM-21S, a

fully synthetic and safe product. Take it off the shelf, don't have to worry about contamination with Bovine contaminants, or with Allograft problems, although that's not a major problem, but it is an issue in patient's minds and some clinicians, so this is fully synthetic and safe as a known mechanism of action demonstrated by over a decade and a half of very intense high quality research a mechanism of action of PDGF. And on the characteristics of the Vitoss, and in fact the Vitoss is a new product developed in 1999.

The recommitant PDGF-BB component enhances periodontic regeneration in animals and humans, and this is very reproducible result seen in many species. I personally have been involved in three dog studies, and they all show the same thing; complete fill of Class 3 furcations. Accelerates attachment level gain and radiographic evidence of bone regeneration, quite well documented in human study I've just mentioned, and demonstrates a favorable risk to benefit relations, so I would say in general, to sum up, my view is that this product

gives a favorable clinical result in 60 to 70 percent of patients when used as indicated with very few side effects that we're not expecting. Thank you very much for your attention.

DR. LYNCH: Thank you very much, Dr. Genco, Dr. Nevins and Dr. Giannoble for those presentations. We had asked the FDA, Mr. Adjodja, Dr. Runner for just a few minutes at the conclusion of the presentation just to be available to answer any burning questions on the methodology. We don't want to pre-empt the discussion this afternoon. We understand there may be some more global questions. I think those might be more relevant for this afternoon, and I think that's where that discussion is planned, but we didn't want to leave any -- if there were any lingering burning questions on methodology or specific aspects of the presentation to let those sort of fester in your mind. So we'd be happy to again entertain any specific burning questions relative to methodology that you might have now, or proceed forward and we can address further questions this afternoon.

CHAIRMAN SUZUKI: Before we begin with the questions, I'd like to remind the audience that I'd like you to reserve any questions regarding the particular hearings until after the presentations. And then secondly, the FDA panel members will have the prerogative of asking questions first, including procedural questions. And I wanted to thank the presenters and the sponsor for presenting such a precise presentation and keeping us on time.

As Chair, I'd like to take the prerogative of asking perhaps the first two procedural questions, and that is with respect to the radiographic benefits - and I know Dr. Genco mentioned looking at the composite outcomes in total, but focusing in on the radiographic interpretations, I notice that there is a mean improvement of about 2.1 millimeters. I'd like an explanation as to why you think that this is clinically significant.

DR. LYNCH: Okay, certainly. And I'm going to moderate the session and probably defer that to many of our panel members since your question specifically refers to the clinical relevance of the

radiographic bone gain. I think it's appropriate that the clinicians and the panel answer that, and I might refer to Dr. Genco and to Dr. Nevins.

DR. GENCO: The radiograph especially at six months under-estimates the healing. You saw the attachment gain was more like 3.8 with a bone gain for the radiograph of 2.1. I think that reflects the under-estimate. 3.8 millimeters in a 7 millimeter pocket, it's a 4 millimeters gain, 7 millimeters to begin with, you're down to 3 millimeters. And I think we and others have done studies showing that if a pocket is 5 millimeters or greater, it has a 6 to 7 fold greater chance of losing attachment in the next two years, so if you can get it below 5 or 6, that bodes well for the future. And I think this is what this study has shown, that the pockets are reduced from 7 to approximately 3, 3 and a half. The bone doesn't quite reflect that because it under-estimates the healing, but the pocket reduction and the attachment gain I think really are telling from the clinical standpoint.

CHAIRMAN SUZUKI: Okay. Thank you. My

second question is a procedural one regarding the surgery itself. In the video clip that we saw, there were just a couple of procedure questions that I had. The first is that in your presentation of materials, you indicated that you use Tetracycline of the preparation of the root surface, but the video clip did not show that. Is there a reason why it was omitted or was that standardized?

DR. LYNCH: Yes, and Dr. Giannoble, who was an investigator, could comment, but I could certainly comment on that one, as well. It was omitted from the video clip simply to make that a very concise video clip for no other reasons. It was standardized as to the amount of Tetracycline that was used and the duration of the root conditioning so that was all pre-specified and the examiners or the surgeons were trained on that.

CHAIRMAN SUZUKI: Okay. The last question I had about the procedure is that frequently surgeons fenestrate the osseous lesion, and I noticed in the video clip that you did not. Was there a reason for selectively not using that particular

step?

DR. LYNCH: Again, Dr. Giannoble, if you want to come up and comment, you could certainly feel free to. We did, I believe, allow fenestration at the discretion of the investigators, a very hard cerotic bone, the bony walls there. It wasn't necessary in the particular case that you saw, but if in the judgment of the investigator that the bone is very cerotic and sort of avascular, it was permitted for them to do perforations.

CHAIRMAN SUZUKI: So that portion of the surgical procedure was not standardized in terms of the fenestration.

DR. LYNCH: Yes, we felt that clinically certainly not all cases would require it, again as the case that you saw, but we felt like certainly some would. So again, in the investigator meeting prior to study initiation, we discussed certainly this very point, and the investigators that we chose, of course, are all very, very highly regarded, very seasoned clinicians, and they felt like you couldn't predetermine that all the lesions should have

perforation because it was necessary in all the lesions, so we discussed the parameters or characteristics of the lesion that would require perforation and left that then to the surgeon.

CHAIRMAN SUZUKI: Okay. AT this time I'd like to ask the panel if they have any points of clarification that they would like answered. And before you do so, I'd like to ask that you identify yourself in the microphone for the transcriptionist, as well as presenters identifying themselves into the microphone, as well, before you respond. Okay. Dr. Cochran.

DR. COCHRAN: David Cochran. Dr. Lynch, I'd like to ask a couple of questions. First of all, in the documentation you provided for us, you used a couple of papers to reference for linear bone growth and percent bone fill. Dr. Genco talked about using the PMAs that were submitted prior for these other products. How did you go about choosing those, particularly there was a study from Greece, and then there was Rutger Persant was another one that you used.

DR. LYNCH: I'll turn this also over to the rest of the panel, but wherever there was data available from the PMA submissions, specifically the summary of safety and effectiveness for previously approved products, we utilized those, so to translate that means Emdogain and PepGen P-15. As has been mentioned, Allograft has never been formally "approved" or cleared for dental uses at any rate by the agency and so, of course, there are no formal FDA submissions that were available, so we did go back through the literature and did a very extensive literature search on specifically looking again at radiographic assessment of bone fill following Allograft treatment. And we used what data was available in the literature. As Dr. Genco mentioned, we're certainly not by any means claiming superiority to any of those materials that were used. We were just trying to, and at the agency's request, get some comparison of the effectiveness of the results seen in this trial benchmarked against other materials that the clinicians are using.

We also utilized or carefully reviewed

the paper out of the San Antonio group that clearly shows that the radiograph assessments do under-estimate bone fill as compared to re-entry assessments.

DR. COCHRAN: That was a good choice. The second question is what are your thoughts on comparing some of your results to the enamel matrix proteins being that that's a protein-only therapy, and you're using protein plus graft material. Would you comment on that?

DR. LYNCH: Again just to stress that the comparisons that we did were simply to compare the results to other benchmarks of effectiveness that were available. The TCP that's used as a carrier, as has been mentioned, is fully resorbed within about three to four months and, therefore, we did not think that that would affect, for example, the radiographic assessment at six months, as was mentioned. That's one reason we did not do the radiographic assessment at three months.

Given that the PDGF is clearly gone by six months, given that the matrix is, as far as we

can determine, certainly mostly, if not totally, resorbed at six months, as well; that would make that site then somewhat comparable, and I don't want to overstate this to the Emdogain where there was no matrix observed.

We know in clinical practice that many people do mix Emdogain, as again has been investigated in your university, with other bone substitute materials to try to contain it in the bone defect. And I think that that was one of the rationales for using a matrix in our product, was to provide the clinician a standard matrix that they could use to mix with the recombinant protein, as compared to Emdogain where the clinicians are often just kind of taking whatever they have on the shelf, so to speak, or whatever grafting material they like and mixing it with the Emdogain, so we feel this provides a more standardized product.

DR. COCHRAN: The last question would be in the documentation there's a product mentioned called Vitoss Plus, which is a similar product or an approved product. What is that?

DR. LYNCH: It's just a different name that -- sorry for the confusion there. Actually, the names of this product that we're reviewing today have sort of transitioned from Beta TCP Plus, at some point I think in the documentation it was called Vitoss Plus, now it's called GEM-21S. It's the same product.

CHAIRMAN SUZUKI: Dr. Amar.

DR. AMAR: Salomo Amar. I'm going to ask a more general question. Dr. Genco mentioned that at a certain point the control catches up with the rest of the experimental. And my general question, if at six months the control or the experimental -- the control catches up with the experimental, what would be the added benefit of using this molecule as compared to TCP? Is it just for the early reading improvement parameters or are we talking about long-term maintenance?

DR. LYNCH: Well, Dr. Genco, why don't you come up here and I'll provide my interpretation, but I would like -- I think Dr. Amar would like to hear your's, as well. I think what Dr. Genco was

referring there was for the clinical attachment level of the soft tissue. Certainly, the bone fill as measured radiographically never catches up in the control versus the treatment group, so there's always a strongly significant improvement or benefit in the radiographic bone fill.

DR. GENCO: That's one point. We didn't see that phenomena in the bone. Of course, we only looked at 1.2. With respect to early healing it's, of course, benefit to get that healing pretty much underway in the first three months, and you can get on with the rest of the therapy. We think that if you're involved in a complex case that requires implants and other treatment, that to have this early result at three months is of great benefit, so it's an accelerated treatment that fits in with the treatment of advanced case, and it's a definite benefit.

DR. AMAR: If the clinical attachment level is the primary outcome and it catches up, aside from the bone failing, it looks pretty similar.

DR. GENCO: Well the point is if you --

let's say if you have to put a crown on the tooth, you could start putting the crown on in maybe two to three month rather than waiting six.

DR. AMAR: The other question that I had is regarding the resorption. I saw sections by Dr. Nevins, at nine months I believe on the furcations showing probably some deposit of Beta Tricalcium Phosphate.

DR. GENCO: Myron, do you want to --

DR. NEVINS: If you're referring to the --

CHAIRMAN SUZUKI: Can you identify yourself, please.

DR. NEVINS: I'm sorry. Myron Nevins. If you're referring to the human histology, we didn't use Beta Tricalcium Phosphate. That was an Allograft study. The Allograft was the carrier for that. The only thing I showed with Beta Tricalcium Phosphate was the one slide at the end on a K-9 study, and that was at eight weeks. And on the GEM-21 there was no evidence of Tricalcium Phosphate at all in the control which was the Tricalcium Phosphate by itself.

There were pieces of Tricalcium Phosphate.

DR. COCHRAN: To follow-up on that, I think in that result didn't you get 70 percent regeneration with the TCP alone in that K-9 study?

DR. NEVINS: I would have to --

DR. COCHRAN: It's 37 percent, not 70.

DR. NEVINS: It's the blue column over TCP.

CHAIRMAN SUZUKI: Okay. Any other questions, Dr. Cochran? Okay. Any other questions from the panel? Dr. Sharma.

DR. SHARMA: According to the protocol, this is Inder Sharma. According to the protocol, the primary comparison was to be between the high dose and the control. Only if it was significant, then 0.3 which is low dose, was to compare with control. But I see the focus of presentation have been mostly on the low dose, so I'm wondering what happened that we are now focusing on what we said in the protocol that this will be about primary comparison, because primary comparison is not significant whether you look at three months or six months.

DR. LYNCH: I think you're looking at an older version of the protocol. There were formal amendments that were submitted to the agency and approved by the agency throughout the study for various things that we had under discussion with them, so the primary comparitor was the .3 mg/ml dose level versus the TCP control.

DR. SHARMA: The second question I have is about the composite end-point. Was this a pre-planned comparison or was it decided to do that after the fact?

DR. LYNCH: I'm sorry. I'm not sure I understand your question.

DR. SHARMA: The composite end-point.

DR. LYNCH: Oh, the composite. Okay.

DR. SHARMA: Was it a pre-planned comparison using composite end-point, or was it later decided to be --

DR. LYNCH: I think Dr. Phil Laven will address that. He's our biostatistician.

DR. LAVEN: Hi, Philip Laven, biostatistical consultant to Biomonetics. My company

is Avarion. When we came up with the idea for the composite end-point, it was done before the database lock, and it was planned at the same time that we planned looking at the AUC. That end-point was reflective of the fact that we knew that the disease was more extensive than just looking at the delta CAL measurement, and that the composite end-point had to address both the radiographic end-points, as well as the clinical end-points, so this was all done prospectively before the database lock, but was not in the original protocol.

CHAIRMAN SUZUKI: Dr. Zero.

DR. ZERO: Domenick Zero. I have a question about how the statistical analysis was done, although that's not my main expertise. On looking at the distribution of females, smokers, African Americans, and the CAL values, there are although not statistically significant differences, there are some numerical differences that are noticeable just in looking at the different groups. The data reported, was that an adjusted statistics, or was that just the raw statistic?

DR. LYNCH: Dr. Laven.

DR. LAVEN: Yes, Philip Laven. Those gain that you are seeing there in the report are unadjusted statistics. At the request of the FDA over the last month, we did prepare additional analyses where we did look at controlling for those factors and looking for treatment interactions with factors like smoking, the location of the tooth, whether it was a molar or not, and we did assess those analyses. And those analyses, just to give a sense for where they turned out, there was no treatment interaction with any baseline co-variates, so the treatment advantages that you're materially seeing there, although they're uncorrected, do represent the state-of-the-art for what happened in those groups.

DR. ZERO: Thank you.

CHAIRMAN SUZUKI: Dr. Zuniga.

DR. ZUNIGA: John Zuniga. A couple of very simple, hopefully, questions on the study protocol, just more for clarification. I notice in your management of your post-operative patients, you

included the use of NSAIDs for any analgesia. Was that a -- why did you do that, and do you have concern about NSAIDs in this product?

DR. LYNCH: No. Sam Lynch. There are no specific concerns about NSAIDs related to this product. We just knew that NSAIDs as a general class of drugs had ability to affect wound healing, and we didn't want some patients to be on NSAIDs by some investigators, and other patients not to be, because we thought that that might affect the -- especially the immediate post-op healing, and we did have an end-point that looked at wound healing over that first three week period, so in order to standardize that regimen we just elected not to use NSAIDs.

DR. ZUNIGA: And has that been explored using NSAIDs?

DR. LYNCH: It, again, was not in the pivotal clinical trial. We would have to look at the patients in the human histologic study to see if they were given NSAIDs or not.

DR. ZUNIGA: And then the second question, again relative to the study protocol, is

the antibiotic use and some of the post-operative instructions for the patients. Were there any patients that did not comply with the antibiotics? And if so, were there any difference in effects? And then finally, you have pretty strict protocol for soft foods and diet eating on the other side. How compliant was that regarding effects on the patient outcomes?

DR. LYNCH: Right. I think as is relatively customary, post-op instructions were given to these patients. I don't believe that there were anything unusual about our post-op instructions compared to many that we give our periodontal patients. In terms of any specific, like protocol violations that were reported where the patient reported chewing on the site of the surgery or that kind of thing, and I don't know - Mark, do you care to comment on that? I don't think there was any -- there wasn't certainly any significant violations along that line. There may have been isolated cases.

MR. CITRON: No protocol violations.

DR. LYNCH: Okay. So there were no protocol violations.

CHAIRMAN SUZUKI: I have a couple of final questions. With respect to the dose, .3 versus 1.0 milligrams per mil, were dose response curves completed prior to your selection of these doses, or were these doses taken from the literature? And secondly, why isn't more better?

DR. LYNCH: I think the second half of your question, Dr. Suzuki, we might want to table to this afternoon. It's certainly a very excellent question, and I don't mean to put it off. We could address it here, but for broader questions in terms of that, we might defer those to this afternoon at your discretion.

In terms of how we selected the .3 and the 1 mg/ml, as Dr. Giannoble showed one slide from the study by how co-workers at Harvard and UNC several years ago, that study utilized .05 mg/ml, and a .15 mg/ml of PDGF. And then that study used also accommodation with the insulin like growth factor, and it showed that there was no effect, no beneficial

effect at the .05 mg/ml. There was a significant beneficial effect on bone similar to what we frankly saw in this study at the .15 mg/ml, so we used that as information. We also then conducted a canine study that looked at the .3 mg/ml, and you say well how did you get from .15 mg/ml in that initial clinical study a few years ago to .3. And the rationale, right or wrong there was that because that initial study utilized a combination of two growth factors, we felt like we might need to utilize the total growth factor dose, if you will, and so that would be .3 mg/ml. So that was the justification for the low dose in our pivotal trial. And the justification for the high dose was taken just as a XXX multiple from that. And as was reported, I believe by Dr. Nevins, we did see absolutely consistent results in the canine study that the .3 mg/ml provided the most beneficial response, so that was again the reason for determining that that was our primary comparitor, was based upon the canine study.

CHAIRMAN SUZUKI: Thank you. John Suzuki

again. My last question is with respect to the T-inclusion criteria, and the age range of your periodontitis patients were from age 25 to 75, I believe. In the submitted materials, you indicated that the aggress of periodontitis patients were excluded from this patient group; yet in the oral presentation that was not in the particular slide. Is there a reason for that?

DR. LYNCH: Sam Lynch. That was just omitted off the slide just for sake of brevity, and we couldn't include all of the criteria on the slide. But certainly, patients that were considered to have aggressive periodontitis, what we used to call juvenile periodontitis, were excluded from the study.

CHAIRMAN SUZUKI: Dr. Amar.

DR. AMAR: I have just one more question. You're going to do x-ray analysis and Dr. Genco mentioned that there was no stent, am I correct? There as no stent. And what was the percentage of elongation accepted, and you mentioned 15 percent. Am I correct?

DR. GENCO: I can start the answer. Bob

Genco. Maybe Dr. Reddy can continue. But what I presented was that the elongation -- or for shorthand, 15 percent, it was seen in less than 5 percent of the x-rays. Is that the question?

DR. AMAR: I guess my question is if it's really 15 percent, the cut-off value on a tooth that's -- a root that is say 10 millimeters, 15 percent is 1.5 millimeters, that the effect size - it's about the effect size that we would see on bone fill. And I would have some kind of concerns about that.

DR. GENCO: Well, that was used to then adjust the x-rays to normalize.

DR. AMAR: So there was no more than 5 percent elongation.

DR. GENCO: Well, let's let -- well, 5 percent of the cases exceeded the criteria of 15 percent elongation or foreshortening. Therefore, required normalization, so the extent to which there were over 15 percent - I think that Mike could answer that. Dr. Reddy.

DR. REDDY: I think I understand what

Salomo is asking. Hi, Michael Reddy. I'm an investigator from the University of Alabama. I did radiograph analysis. You want to know what percent -- what was the highest range of elongation and foreshortening. And I have to look at the database to tell you exactly, but some of them were up to about 25 percent, but there were very few x-rays. Remember, this was an intent to treat analysis, so we simply couldn't say that that didn't make our radiographic criteria, so we included them, and then retrospectively corrected it mathematically. You have to remember that a 15 percent increase in the overall root length, which may be 15 millimeters in length, may just vary the measurement of the bone growth by about 10 percent even if you didn't correct for it, even though we did correct for it. So if you have 2 millimeters of bone growth, you're really only going to change it to about 2.2. But the case that did happen, we did mathematically apply a formula and run an algorithm to correct those. Those are very few. We had a great fear, the same fear you had at the start of the study. That's why we incorporated

that into the analysis, this 15 percent cut-off because we were afraid that these are field x-rays, and we may have 50 percent of them with elongation and foreshortening, and it turned out that they were actually very clinical radiographs. Of course, again, we had to get a good x-ray of one tooth --

DR. AMAR: So if I understand you correctly, there was an area of elongation about 15 percent of max that was corrected.

DR. REDDY: No, only if the area was over 15 percent was it corrected. There were some sites that were 25 percent foreshortened or elongated.

DR. AMAR: That could translate into if the root is 10 millimeters into 1.5 millimeters change?

DR. REDDY: It could if it wasn't corrected for, and that's the reason why we put the correction in, exactly.

DR. AMAR: Can you elaborate on the correction?

DR. REDDY: Yes, the correction simply to go ahead and correct everything back to the baseline.

We consider whatever length we measured at the baseline from CEJ to apex as the gold standard. If it differed by more than 15 percent, we used a ratio of the original CEJ to apex measurement to new CEJ to apex measurement to mathematically correct all measurements that were subsequently taken, so we wouldn't lose the data.

DR. AMAR: Thank you.

DR. SHARMA: I have one.

CHAIRMAN SUZUKI: Okay. Dr. Sharma.

DR. SHARMA: Inder Sharma. I have one final question. Interim analysis were planned for the study and I was wondering where they conducted? And if they were conducted, was there a DSMB or who had access to those results?

DR. LYNCH: Would you mind repeating the question, please?

DR. SHARMA: The interim analysis for the study --

DR. LYNCH: Interim analysis --

DR. SHARMA: They were planned, and my question is if those interim analysis were conducted,

and who had access to the results, was it a DSME independent diversity of monitoring the worker?

DR. LYNCH: Yes, I understand. Sam Lynch. There was an interim analysis conducted per the protocol. The analysis was conducted on the first 90 patients to complete three-month follow-up. This was, again, an analysis that was agreed upon with the agency. It was done in a fully blinded fashion by the independent clinical research organization, the CRO that was responsible for monitoring the study, so there certainly was no breaking of the blind or anything.

The only data that we got back was that and the reason the FDA had asked us to do that interim analysis was to one of sample size, should we adjust the sample size at that point? Do we increase the number of patients, because we had agreed not to decrease the number of patients because we did not want to take a statistical penalty for the interim analysis, so we had all along said we're going to do 180 patients, even if that result was just fantastic. But the question was would we need to add patients