SUMMARY MINUTES

MEETING OF THE DENTAL PRODUCTS ADVISORY PANEL

OPEN SESSION

July 13, 2004

Gaithersburg Hilton
Gaithersburg, MD

Dental Products Devices Advisory Panel Meeting

July 13, 2004 Open Session

Attendees

Chairperson
Jon B. Suzuki, D.D.S., Ph.D.
Temple University

Executive Secretary
Michael E. Adjodha, M.ChE.
Chemical Engineer
Dental Devices Branch

Voting Members
David L. Cochran, D.D.S., Ph.D.*
University of Texas Health Sciences Center, San Antonio

Salomon Amar, D.D.S., Ph.D.
Boston University School of Dental Medicine

William J. O'Brien, M.S., Ph.D.*
University of Michigan School of Dentistry

Domenick T. Zero, D.D.S., M.S.
Indiana University School of Dentistry

John R. Zuniga, Ph.D., D.M.D.
University of North Carolina School of Dentistry

Consultants
Inder J. Sharma, Ph.D.
Morehouse School of Medicine

Consumer Representative
Elizabeth S. Howe
National Foundation for Ectodermal Dysplasias

Device Industry Representative
Daniel R. Schecter, J.D.
Parkell, Inc.

Drug Industry Representative
Alison F. Lawton, M.B.A.
Genzyme Corporation

FDA Participants
M. Susan Runner, D.D.S., M.A.
Captain, USPHS
Deputy Division Director, DAGID and Chief, Dental Devices Branch

Angela E. Blackwell, M.S.
Biomedical Engineer
Dental Devices Branch

Judy S. Chen, M.S.
Mathematical Statistician
Division of Biostatistics

* Waiver allows panel member to participate in discussion but not vote.

CALL TO ORDER

Panel Chair Jon B. Suzuki, D.D.S., Ph.D., called the meeting to order at 8:30 a.m. **Executive Secretary Michael E. Adjodha, M.ChE.**, introduced the panel members and stated that Inder J. Sharma, Ph.D., had been appointed to temporary voting status. He then read the conflict of interest statement; waivers had been granted for Drs. Cochran, O'Brien, and Sharma for their interests in firms that could potentially be affected by the Panel's recommendations. Dr. O'Brien's and Dr. Cochran's waivers allowed them to participate in the panel discussion but exclude them from voting. Dr. Sharma's waiver allowed him to participate fully. The Agency took into consideration certain matters involving Dr. Zero, who reported past and current interests in firms at issue but in matters not related to the day's agenda, and determined that he could participate fully.

Dr. Suzuki noted that the voting members present constituted a quorum.

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No comments were made.

SPONSOR PRESENTATION

Mark Citron, Vice President for Regulatory Affairs, BioMimetic Pharmaceuticals, introduced the sponsor presenters and consultants and summarized the sponsor's agenda.

Samuel Lynch, D.D.S., noted that the meeting is the culmination of 15 years of research and summarized the development history of the GEM21S product. GEM 21S consists of two components: (1) beta tricalcium phosphate (ß-TCP) in a cup and (2) a physiologic solution containing recombinant human platelet-derived growth factor (rhPDGF-BB) packaged in a syringe. After mixing the two components, the material forms a mass of particles which are then packed into the bone defect. rhPDGF-BB is an FDA-approved wound-healing agent that has been on the market for 5 years. More than 200 publications on rhPDGF-BB describe its effects on wound healing; the literature includes findings on both in vivo and in vitro research. The material has a good safety record. ß-TCP is an FDA-cleared bone augmentation device.

GEM 21S is a fully synthetic bone regeneration system supported by years of research. It has a known mechanism of action and has been demonstrated to be safe. The rhPDGF-BB component enhances periodontal regeneration in animals and humans, accelerates attachment-

level gain, and improves radiographic evidence of bone regeneration. The product has a favorable risk-benefit ratio.

William Giannobile, D.D.S., DMSc., University of Michigan, clinical investigator, presented the sponsor's preclinical data. Many factors are critical to the regeneration of diseased periodontium. Given that tooth root structure is avascular, it is critical to create an environment that promotes blood supply. ß-TCP is an osteoconductive matrix for bone formation. It prevents soft-tissue collapse and facilitates blood clot stabilization. rhPDGF-BB is chemotactic for bone and periodontal ligament (PDL) cells, mitogenic for bone and PDL cells, and angiogenic.

ß-TCP is a synthetic, purified, resorbable, porous calcium phosphate resembling bone mineral. It is an FDA-cleared osteoconductive bone void filler that has a good history of use and is currently marketed for orthopedic and dental applications. In more than 20 years of commercial use, no adverse events have been reported to the FDA's MDR database. The material was recently recommended to be downclassified toClass II. ß-TCP's 90-percent open pore structure allows cellular ingrowth and vascular invasion.

rhPDGF-BB is an extensively characterized endogenous protein. It is a natural wound-healing hormone that operates by enhancing connective tissue formation, osteogenesis, and angiogenesis. rhPDGF-BB and its receptors are naturally induced during normal tissue and bone repair. It is chemotactic for PDL and gingival fibroblasts and osteoblasts and is mitogenic for PDL and gingival fibroblasts, cementoblasts, and osteoblasts. rhPDGF-BB promotes matrix biosynthesis by PDL and gingival fibroblasts and osteoblasts. The material supports cell survival and enhances angiogenesis by promoting smooth muscle cells around new blood vessels, complementing vascular endothelial growth factor (VEGF) for blood vessel maturation, and increasing VEGF production by osteoblasts. It has been found to stimulate in vitro wound repair, and it retains its bioactivity even when released from TCP.

Results from an in vivo study in beagles found that rhPDGF-BB in combination with guided tissue regeneration (GTR) resulted in greater periodontal bone repair than GTR alone. It promoted a three- to fivefold increase in cellular DNA synthesis. rhPDGF-BB strongly augmented the degree of new bone and periodontal ligament, and it blocked scar formation and granular tissue. In an osteoporosis model, rhPDGF-BB resulted in significantly greater trabecular bone density compared with control. Numerous studies show the ability of rhPDGF-BB to promote bone growth and tissue regeneration.

The components of GEM 21S have an extensive safety track record. Safety of rhPDGF-BB has been demonstrated in multiple clinical trials and 5 years of commercial use. Patients have received daily dosing for up to 140 days. No neutralizing antibodies result from its use. More than 17 million dose units have been prescribed worldwide. Confirmatory safety tests following FDA and EU standards have all shown GEM 21S to be biocompatible and safe.

Myron Nevins, D.D.S., Harvard University, stated that periodontal regeneration consists of formation of new bone, new cementum and new PDL to form a new functional attachment apparatus. The process occurs over a pathologically exposed root surface. A histology study in humans involved 11 intraosseous defects around teeth scheduled for extraction: six intrabony and five Class II furcation defects. The defects were treated with rhPDGF-BB plus allograft. The teeth and surrounding tissue were extracted at the 9-month point, and histologic analyses were conducted. Pocket depth, CAL, and bone height all improved significantly from baseline. The rhPDGF-BB stimulated tissue regeneration in intrabony defects, including new cementum, ligament, and bone, and it stimulated regeneration in Class II furcations. The results demonstrated safety and normal bone and ligament remodeling. Clinical measurements were significantly improved. Radiographs were consistent with bone fill, and no

evidence of root resorption or ankylosis was found. Histologic evaluation revealed regeneration in intrabony and Class II furcation defects.

Synthetic ß-TCP and allograft provide comparable delivery of rhPDGF-BB, but FDA has not formally approved allograft. Results from a canine histology study comparing in vivo performance of rhPDGF-BB with either ß-TCP or allograft carrier found that the rhPDGF-BB/ß-TCP combination produced better results than the rhPDGF-BB/allograft combination.

GEM 21S is safe and biocompatible. rhPDGF-BB used in combination with ß-TCP or allograft significantly improves periodontal regeneration (including bone, cementum, and PDL). The preclinical research produced sufficient evidence to initiate the pivotal clinical trial.

Robert Genco, D.D.S., SUNY Buffalo, described the pivotal study design and methodology. The study was a double-blind, prospective, randomized controlled trial involving 180 patients in three treatment groups. Group I received ß-TCP plus 0.3 mg/mL rhPDGF-BB; Group II received ß-TCP plus 1.0 mg/mL rhPDGF-BB, and Group III received ß-TCP plus a buffer solution. Clinical and radiographic endpoints were evaluated at baseline and 6 months. The study involved an active control in that the product is already on the market for orthopedic use. The examiners were a separate group from the surgeons, and they were calibrated at baseline and 6 months to ensure reproducibility and consistency across sites. The study was independently monitored for quality and safety, and data were independently analyzed by Target Health, Inc.

Patients were between ages 25 and 75, had pocket depth of at least 7 mm, and had bone defect of at least 4 mm. Grade I and II furcations were allowable, and smokers of up to 1 pack per day were permitted to enroll. Outcome measures included clinical attachment level (CAL), linear bone growth (LBG), percent bone fill (%BF), pocket depth reduction, gingival recession,

wound healing, and comparison to current therapies. A composite outcome consisting of clinical and radiographic data also was used. The surgical technique was standardized.

Radiographs were taken under uniform high-quality field conditions. Films were digitized, and linear measurements were obtained at the University of Alabama–Birmingham using standard techniques and validated LBG and %BF measurements. Radiographic assessment was adjusted if the radiograph demonstrated foreshortening, which occurred in less than 5 percent of the cases.

No device-related adverse events occurred; pain following surgery was the main adverse event. The product significantly improved CAL; the CAL gain, as assessed by area-under-the-curve (AUC) analysis, was maintained at 6 months. The product also resulted in significant LBG and %BF. The results exceeded benchmarks of effectiveness including Emdogain, PepGen P-15, allograft, and OFD. No significant differences were observed among the three treatment groups in terms of baseline defect characteristics.

Dr. Genco presented graphs comparing CAL gain for different doses and comparing GEM 21S with other therapies, which showed that GEM 21S at a dose of 0.3 mg/mL produced greater CAL gain than other GEM 21S doses and other therapies. AUC analysis was used to detect differences in CAL gain between baseline and 6 months. One subject had abscess but was not removed from analysis. The *P* values were powerful. Similarly, GEM 21S at a dose of 0.3 mg/mL produced greater LBG and %BF than other GEM 21S doses and other therapies.

Finally, the sponsor used a composite endpoint consisting of CAL and LBG, two primary endpoints that are recommended for establishing effectiveness in periodontal wound healing trials. For both the CAL/%BF and the CAL/LBG composite endpoints, GEM 21S at a dose of 0.3 mg/mL produced better results than other GEM 21S doses and other therapies.

GEM 21S is a fully synthetic and safe product. It has a known mechanism of action, which has been demonstrated through more than 15 years of research. rhPDGF-BB enhances periodontal regeneration in animals and humans, and the product accelerates CAL gain and bone regeneration. The product has a favorable risk-benefit profile and should be approved.

Panel Questions for Sponsor

Panel members asked for clarification as to the clinical significance of the radiographic images; the use of tetracycline and lesion fenestration during the surgery; the rationale for the supporting literature that was selected; the product's effectiveness compared with matrix growth proteins; the relative benefit of the product in light of the fact that the control group caught up with the treatment group at 6 months; the retrospective introduction of the composite endpoint; the impact of different patient factors, such as smokers versus nonsmokers; any dose-response curves for the product; the process for correcting foreshortening on the radiographs; and the process for and timing of the sponsor's interim data analysis. Sponsor representatives provided additional information to the panel's satisfaction.

FDA PRESENTATION

Dr. Runner introduced the FDA presentation and speakers. She noted that the Agency had received additional information that would not be discussed at the meeting because the Agency had not had time to review it.

Angela E. Blackwell, M.S., Biomedical Engineer, Dental Devices Branch, presented information on the regulatory history of the components of GEM 21S. ß-TCP is regulated as a

Class II device, and rhPDGF-BB requires a biological licensing agreement. ß-TCP is marketed for orthopedic indications as Vitoss under a 510(k) and is also regulated as a dental device.

Dr. Runner reviewed the safety data, which was based on data from studies on use of rhPDGF-BB in foot ulcers as well biocompatibility studies, previous clinical data, and FDA database information. Effectiveness data from preclinical and feasibility studies indicate that GEM 21S may be effective for the sponsor's stated intended use.

Dr. Runner then reviewed the clinical study methodology, including treatment groups, measurements, and endpoints. The primary endpoint was change in CAL at 6 months; the other endpoints were secondary. The sponsor retrospectively added 3-month CAL, LBG, and %BF endpoints after the data were collected. The sponsor also included secondary endpoints comparing historical data from PMAs for Emdogain (which is not a bone grafting material) and PepGen. The numbers are averages derived from literature. In addition, the sponsor added two composite study outcomes and an AUC analysis.

In Group I (low dose), the results for the prospective primary endpoint were not statistically significant, although results for the secondary endpoints gingival recession, LBG, and %BF, as well as for the retrospective endpoints, were significant. For Group II (high dose), the only significant results occurred with the LBG and %BF secondary endpoints. No adverse events were attributable to GEM 21S, a finding that is consistent with other studies. The study was followed without protocol violations, and the Agency has no safety concerns.

The study failed to meet its primary efficacy endpoint, although results for many secondary endpoints demonstrated statistically significant results. Retrospective analyses were positive for the low-dose group at 3 months. Agency concerns include the sponsor's reliance on

secondary endpoints and retrospective statistical analyses, the uncertain clinical benefit of rhPDGF-BB, and the sponsor's request to expand the indications for use.

Judy S. Chen, M.S., Mathematical Statistician, Division of Biostatistics, reviewed the study hypothesis and methodology. The data indicate that statisticians can reject the null hypothesis that adding rhPDGF-BB to ß-TCP will improve 6-month CAL, as long as the false positive rate is under control. However, based on the data, the false positive rate is 20 percent. The study is inadequately powered, and 750 patients would be needed to give it adequate power to detect the small treatment differences involved. In addition, results based on endpoints constructed after blinding is broken are not reliable. The Agency's statistical analysis concluded that the data do not demonstrate that adding rhPDGF-BB to ß-TCP statistically significantly increases CAL, the primary endpoint. Statistically significant benefit occurred for the secondary endpoints of %BF and LBG, however. The treatment effect found in the two composite endpoints is not reliable because the false positive rates are inflated and cannot be statistically adjusted.

Panel Questions for FDA

Panel members and Agency representatives discussed the timing of and rationale for the sponsor's data analysis. Ms. Blackwell stated that none of composite endpoints were provided until the PMA was submitted; that is, the endpoints were not prospective. The original protocol called for gathering CAL data at 3 months, but not as a primary endpoint; only the 6-month endpoint was primary. The sponsor asked for changes in the course of the study. The change in dose happened before the data were unlocked but after the original study was approved. The

Agency asked the sponsor to perform a metaanalysis with published data because the primary endpoint was shown to be not significant.

The sponsor clarified that at the time of its submission last summer after the data were collected, the database was still blinded. The sponsor never broke the blind for the analyses. Only after the integrity of data was assessed did the sponsor unblind the data.

Panel members asked for clarification as to whether the sponsor compared results for low and high doses of the product, and they discussed the validity of the sponsor's one-sided test for significance, the validity of the secondary endpoints, the clinical significance of the sponsor's results for LBG, the retrospective use of secondary endpoints as primary endpoints, and the validity of the radiographic data. The panel had many questions on data collection, the appropriateness of the composite endpoints, and the sponsor's apparent retrospective analysis.

PANEL REVIEWS

Salomon Amar, D.D.S., Ph.D., panel reviewer, stated that the product is safe, but efficacy is a concern. Some kind of clinical significance results from adding rhPDGF-BB to ß-TCP, whether in terms of early wound healing or in linear bone measurements and bone fill. Increased bone growth helps tooth longevity. The trial was well conducted. If the desired outcome is regeneration per se, then clinical significance is unequivocal. If closing of the pocket is the desired outcome, clinical significance exists at 3 months, but it does not last: The ß-TCP-only group also closed at 6 months, but without bone support. CAL is clinically significant at 3 months, but it is not different from controls.

Another concern is that the sponsor provided comparison of Groups I and II. Linear measurements were better for participants receiving the low dose, which raises a concern as to

whether practitioners should use several doses for several adjacent areas, thereby increasing the local concentration. Adverse events and other risks are not an issue.

In general, the benefits of the device outweigh the risks. The clinical study data lack information as to use of the product in multiple sites on multiple defects and did not include areas for which the device did not perform well. Approval with conditions is appropriate.

Inder J. Sharma, Ph.D., panel reviewer, stated that the product is safe. It is unclear, however, why the lower dose is more effective than the high dose—are there confounding factors related to the study population? A future study with appropriate endpoints and stratification is needed. It is hard to prove efficacy without a larger sample size. The choice of endpoint is important. Effectiveness, but not superiority, was demonstrated.

PANEL QUESTIONS

Question 1: Please discuss the clinical ramifications of the CAL results at 3 months versus 6 months. Panel members noted that the lesions are biologically complicated and many different factors are involved, clouding the significance of the data. The sponsor's endpoint was based on prior PMAs. For products that will stimulate healing, an early endpoint is necessary. A better understanding of the connection between short-term outcomes and the health of the patient, in terms of tooth retention, functionality of tooth, and later susceptibility to disease, would be helpful.

In response to the panel members' concerns, Dr. Runner noted that in periodontal research, the recurrent disease process obscures results after 6 months. Dr. Genco noted that bone loss is a predictor of future bone loss and that pocket closure is predictive of future tooth health. Pocket depth of 5 or 6 mm is predictive of future loss. Dr. Nevins stated that making the

mouth clean without creating a change in the supporting tooth structure will create improvement in CAL, just by reducing inflammation. The goal, however, should be to restore bone that has been lost. Radiographs because are a better indication than CAL of whether healing is going in the right direction. All the sponsor's data indicate overall benefit to the patient.

Panel members also asked for clarification as to whether the patient population in the clinical study was at same risk for periodontal disease as other the wider patient population in which the product will be used. They discussed the fact that the low-dose product was more effective than the high-dose product and expressed concern that use of multiple units in a single patient was not addressed in the sponsor's submission. Sponsor representatives noted that in the study, the operators never had to use more than one package.

Question 2: Please discuss the validity and clinical significance of relying exclusively on the secondary endpoints and retrospective analyses, identified by the sponsor, for approval of this PMA. Panel members stated that it is important to consider the control in the trial. Much literature suggests that most bone graft material will generate a good response. The chance to distinguish a difference by adding a protein is small. The secondary outcome variables are highly clinically relevant.

Question 3: In the PMA, the sponsor is requesting approval for the following intended uses: periodontal disease, cystectomy, apicoectomy, deficient alveolar ridges, and tooth extraction sites. Are these claims supported by the data and information submitted? Panel members noted that the sponsor had not provided subgroup analysis for patients with special healing issues, such as the elderly and diabetics. They expressed interest in evidence of

how the product behaves in different environmental conditions. Panel members were concerned about the lack of data supporting the expanded indications and the potential for irritation of nervous tissue if the product is used for the expanded indications. One panel member expressed concern that use of the product for deficient alveolar ridges, and tooth extraction sites could stimulate ligament in bone sites, but Dr. Runner noted that in PMAs for similar products, such indications are common.

Sponsor representatives responded to the panel members' concerns by stating that in an osteoporosis model, statistically strong benefit was obtained by adding rhPDGF-BB throughout the skeleton. In addition, subgroup analyses by age had been recently submitted to the Agency (it was not presented to the panel because the Agency had not had time to review the information). Those results showed consistent advantages to use of the product. rhPDGF-BB in general is a stable protein, particularly in acidic environments. It appears to be more stable than other molecules. The list of indications was drafted to resemble the indications that have already been allowed for ß-TCP, and the addition of rhPDGF-BB should not limit labeling. No adverse events involving nervous tissue have been seen with Granax, which includes rhPDGF-BB and is used in treatment of severe skin wounds involving subcutaneous tissue and would expose patient to many of those considerations. Granax has been shown to be safe and effective in a severely diabetic population.

Question 4: Does the information submitted by the sponsor provide a reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling? If the data and information submitted do not provide reasonable assurances of safety, what information is needed to establish safety for the claimed

intended use? Panel members had no additional comments to supplement their earlier discussion.

Question 5: Does the information submitted by the sponsor provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling? If the data and information submitted do not provide reasonable assurances of device effectiveness, what information is needed to establish safety for the claimed intended use? Panel members noted that the clinical study demonstrated effectiveness, but not for all the proposed indications for use. Future research should consider composite endpoints involving measures of linear bone height and other bone parameters, although those measures do not necessarily correlate well with histologic data.

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No comments were made.

FDA CONCLUDING COMMENTS

Dr. Runner thanked the panel for its input.

SPONSOR CONCLUDING COMMENTS

Dr. Genco thanked the panel and clarified the timing of the data analysis. The endpoints specified prior to the database lock were CAL, LBG, %BF, gingival resection, pocket depth reduction, wound healing, and CAL AUC (post hoc). Analysis was completed before the data

blinding was lifting. Endpoints analyzed after the database lock were the composite analyses (using only 6-month data) and the metaanalyses requested by FDA.

PANEL VOTE

Executive Secretary Adjoudha read the voting options. The panel voted unanimously (4-0) that the device was approvable with the following conditions:

1. The labeling must not make claims to superiority on the basis of the primary endpoints.
2. The indications for use should be restricted to periodontal or periodontal-related defects because of the lack of safety data on use with nonperiodontal tissues.

Dr. O'Brien suggested that the instructions for use should clarify the amount of pressure to use in inserting the product. Mr. Schecter, the industry representative, said that the study was a model of cooperation between FDA and the sponsor.

POLL

In explaining the rationale for their votes, panel members stated that they believed GEM 21S was as effective as products currently on the market. Regeneration of supporting bone structure is important, and GEM 21S will help accomplish that goal. The product is safe, and the animal model and clinical data are convincing as to efficacy. The product is based on two other FDA-approved materials with long histories of use.

ADJOURNMENT

Dr. Suzuki thanked the participants and adjourned meeting at 3:01 p.m.

I certify that I attended this meeting of the Dental Products Advisory Panel on July 13, 2004, and that these minutes accurately reflect what transpired.

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Michael E. Adjodha, M.ChE.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Jon B. Suzuki, D.D.S., Ph.D.
Chairperson

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