GEM 21S®

Growth-Factor Enhanced Matrix

LYNCH BIOLOGICS LLC

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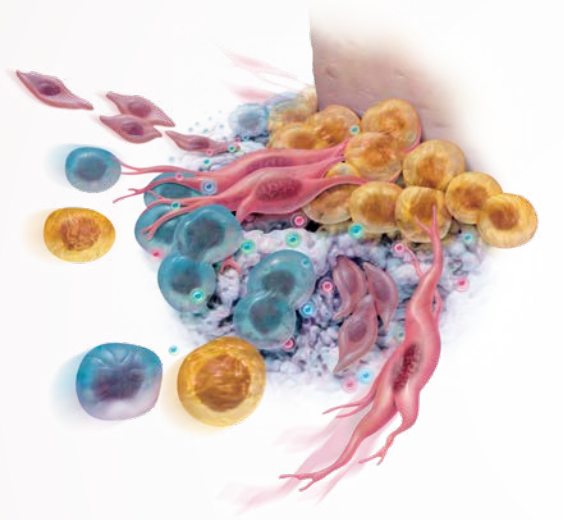
GEM 21S® Growth-factor Enhanced Matrix was developed utilizing innovative tissue engineering principles which combine a bioactive protein (highly purified recombinant human platelet-derived growth factor, rhPDGF-BB) with an osteoconductive matrix (beta tricalcium phosphate, β-TCP).

This completely synthetic grafting system is engineered to stimulate wound healing and bone regeneration when implanted in the body by triggering a cascade of molecular events that continues on even after the implanted PDGF is gone.

Mechanism of Action

PDGF is released from the β-TCP matrix into the surrounding environment. PDGF then binds to specific cell surface receptors on target cells, initiating a cascade of intracellular signaling pathways.



PDGF-induced intracellular events lead to directed cell migration (chemotaxis) and cell proliferation (mitogenesis) of osteoblasts, periodontal ligament fibroblasts and cementoblasts.*

Nature's Wound Healing Agent

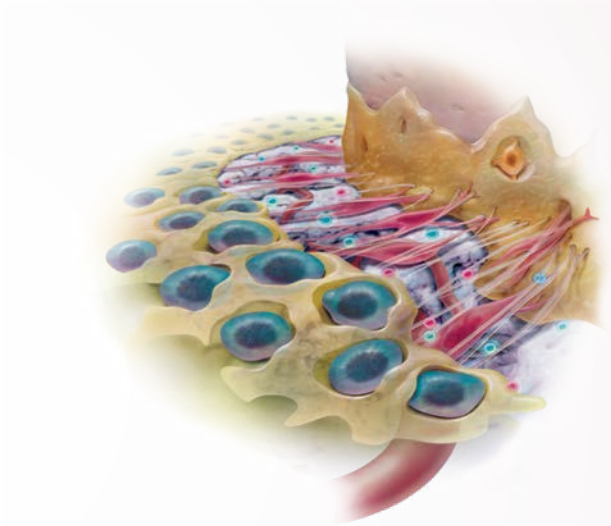
GEM 21S® is the only dental therapy containing PDGF, one of the main growth factors found in the human body and well known for its role in wound healing. PDGF exerts its effects through the recruitment and stimulation of cells within the surrounding tissues.

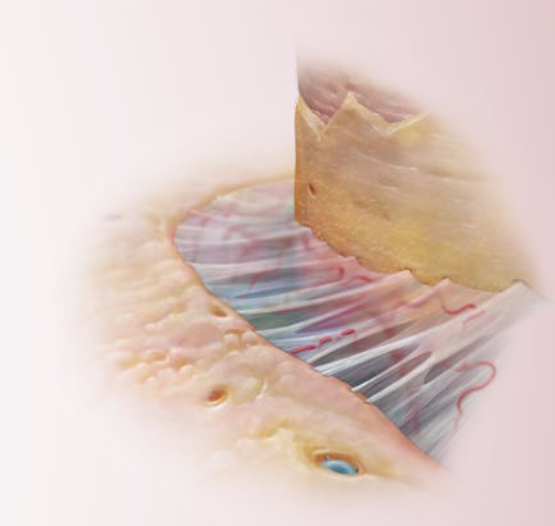
Powerful Stimulant

An adequate blood supply is critical to the success of any grafting procedure. Extensive in vitro and in vivo studies have demonstrated that PDGF-BB is a powerful stimulant of angiogenesis that also stabilizes newly formed blood vessels.

*Based on *in-vitro* and *in-vivo* data; see device description in package insert on pages 16-18 for complete information.

"PDGF significantly increases the proliferation and migration of osteoblasts and other cells of the periodontum" [1, 2, 3]





Proliferation of osteoblasts, periodontal ligament fibroblasts and cementoblasts leads to increased matrix synthesis, resulting in formation of new alveolar bone, periodontal ligament and cementum.* Angiogenesis (blood vessel formation) continues.

Clinical data suggests that over time (approximately 6 months), maturation of supporting alveolar bone, cementum, and periodontal ligament occurs. The end result is enhanced bone and periodontal regeneration and retention of the natural tooth.

"GEM 21S® Growth-factor Enhanced Matrix addresses an unmet clinical need by providing a clear benefit even in the most severe cases where a bone graft alone was found to be ineffective."

FDA's Summary of Safety and Effectiveness

Indications

GEM 21S® is indicated to treat the following periodontally related defects

- Intrabony periodontal defects
- Furcation periodontal defects
- Gingival recession associated with periodontal defects

Please see Full Prescribed Information on page 19.

GEM 21S® Growth-factor Enhanced Matrix is intended for use by periodontists/dentists/oral surgeons familiar with periodontal surgical techniques. It should not be used in the presence of untreated acute infections or untreated malignant cancerous growth at the site of use, where bone grafting is not advisable or tissue coverage is not possible and, in patients with a known hypersensitivity to one of its components. It must not be injected into your body, only placed into a defect in your teeth.

Intrabony and Furcation Defects

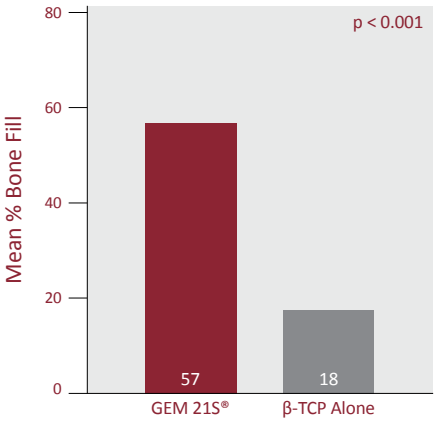
Clinical Performance — Pivotal Trial Data[Package/Insert]

GEM 21S® growth-factor enhanced matrix is a predictable treatment for moderate to severe periodontal defects allowing clinicians the ability to retain patients' natural teeth with confidence.

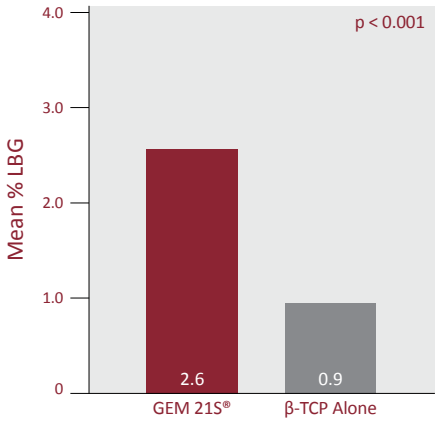
The results of the largest prospective, randomized, triple-blinded and controlled pivotal clinical trial reported to date that assessed a putative periodontal regenerative and wound healing therapy demonstrated the following:

- The use of GEM 21S® was safe and effective in the treatment of periodontal osseous defects
- Treatment with GEM 21S®
  - Stimulated a significant increase in the rate of CAL gain
  - Reduced gingival recession at 3 months post-surgery
  - Improved bone fill and linear bone gain as compared to a B-TCP bone substitute at 6 months

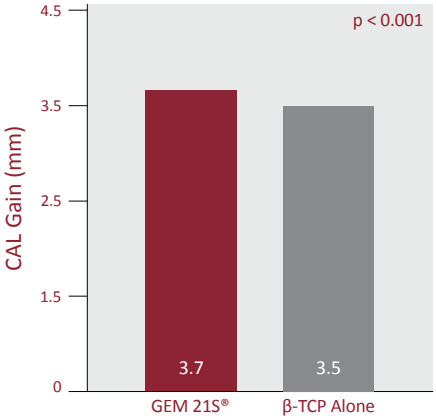
Radiographic Percent Bone Fill



Radiographic Linear Bone Growth



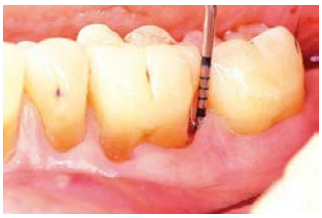
Clinical Attachment Level Gain



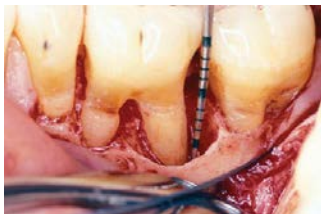
*See Full Prescribing Information on page 19.

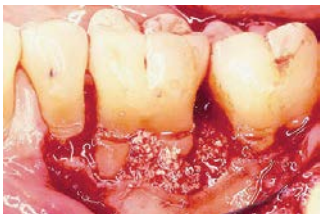
Representative Cases

Case by Dr. Michael McGuire

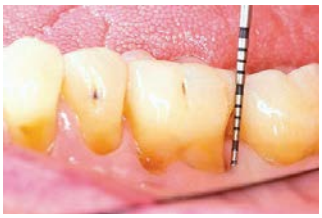


Baseline: 9 mm probing depth and 8 mm deep by 3 mm wide, 2-wall intrabony defect

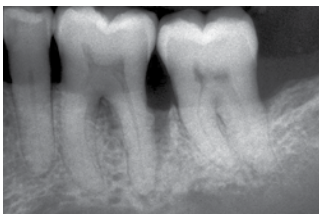




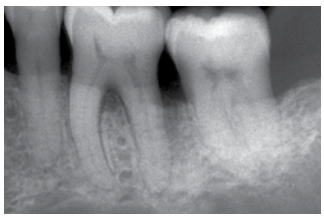
GEM 21S® in place



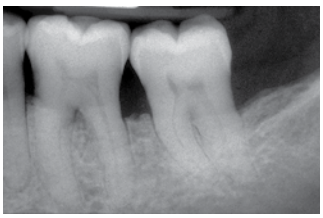
6 months post-op: 3 mm probing depth is observed



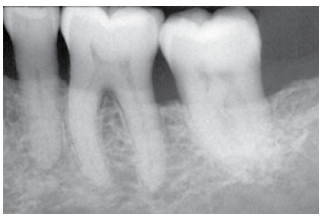
Pre-op radiograph



6 months post-op radiograph: increased radiopacity on the distal surface of the root

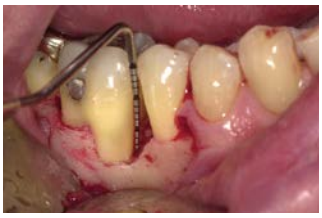


12 months post-op radiograph

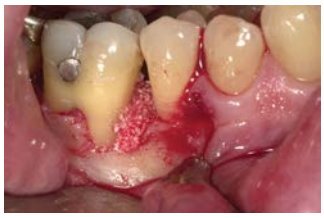


36 months post-op radiograph suggests evidence of further consolidation of bone graft and increasing fill of the furcation

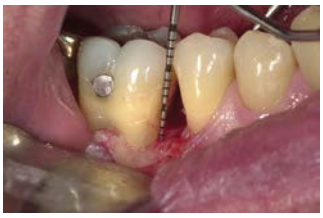
Case by Dr. Brad McAllister



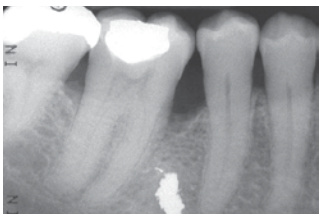
Baseline: 5 mm deep, 3 mm wide, 2-wall intrabony defect



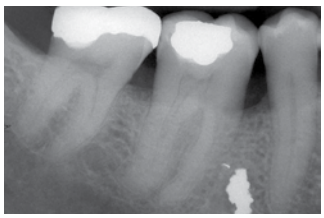
Defect treated with GEM 21S®



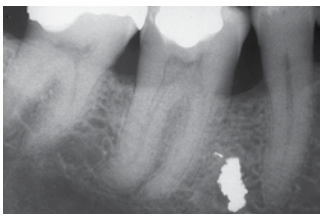
24 months post-op: regeneration of buccal plate across root prominence and complete fill of interproximal defect



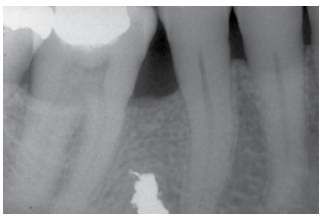
Baseline radiograph



6 months post-op radiograph



12 months post-op radiograph



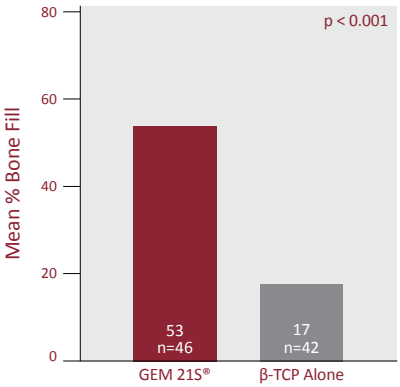
36 months post-op radiograph: normal bone trabecular pattern on the mesial and distal surfaces of the tooth

Clinical Performance in Challenging Cases

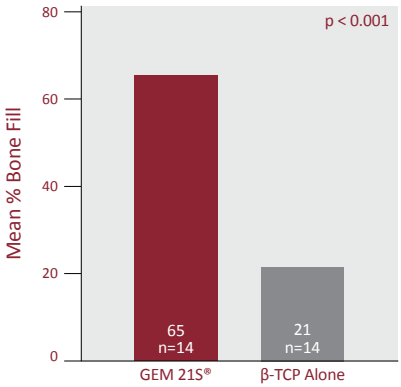
In treating a severe 9 mm 1 and 2 - walled defect with GEM 21S®, significant bone regeneration occurred within the first 9 months post surgery. Treatment with GEM 21S® transformed an almost hopelessly compromised tooth into one that is fully functional with an excellent long-term prognosis.

Case by Dr. Mark Gutt

1 - 2 Wall Defects

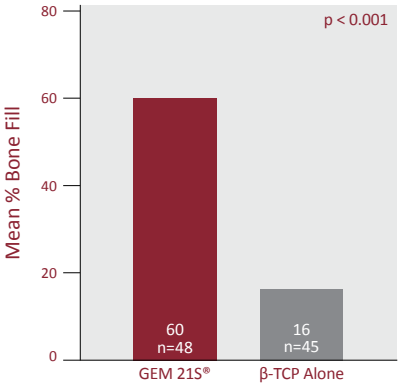


3 Wall and Circumferential Defects

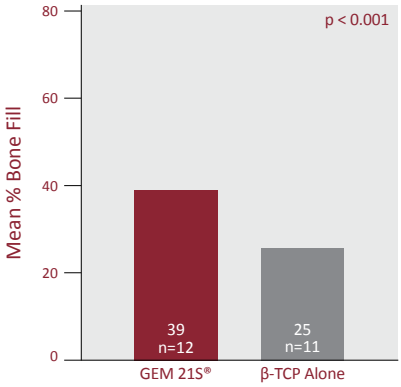


In the 180 pivotal trial that served as the basis for FDA approval, 77% of the defects treated were difficult-to-treat 1 and 2- wall intrabony defects. Within six months, GEM 21S® significantly improved radiographic percent bone fill as compared to β-TCP alone even in the most challenging defects.[4]

Non-smokers

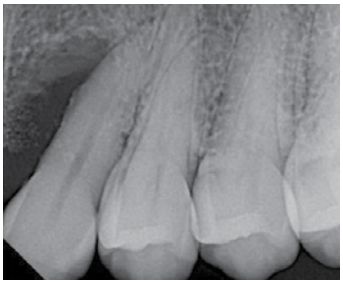


Smokers

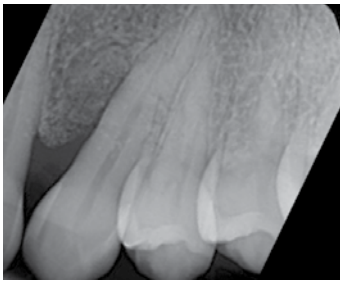


Chronic smoking often significantly compromises periodontal treatment outcomes.* In the pivotal clinical trial, despite smoking up to 1 pack per day, patients treated with GEM 21S® realized significant improvement over those treated with β-TCP alone.

Patient presents with a poor long-term prognosis of tooth #11.



Baseline: 9 mm deep, 1- 2- walled defect between teeth #10 and #11



9 months after treatment with GEM 21S® plus a collagen membrane

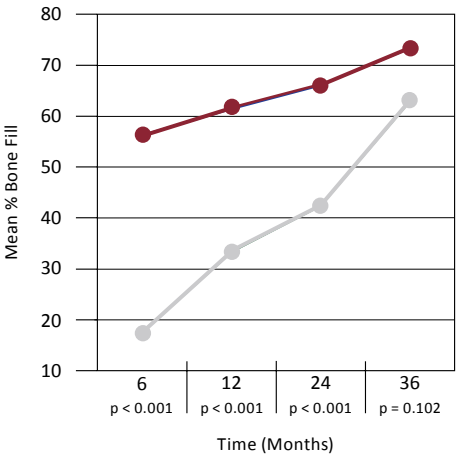
Treatment with GEM 21S® allowed the patient to retain natural dentition and provided a favorable long-term prognosis.

Long-Term Predictability

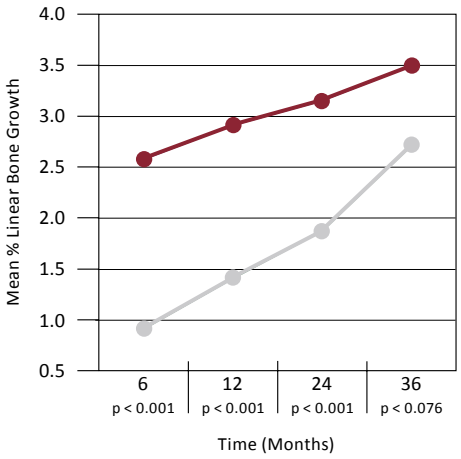
Patients from the GEM 21S® Growth-factor Enhanced Matrix pivotal trial continued to be monitored by their treating physicians for a total of 36 months. The data collected demonstrates the continued long-term efficacy of GEM 21S® treatment.

- The GEM 21S® group demonstrated significantly more bone fill over the β-TCP control throughout 36 months
- It took more than 2 years for the β-TCP group to reach the level of bone fill achieved with GEM 21S® in only 6 months

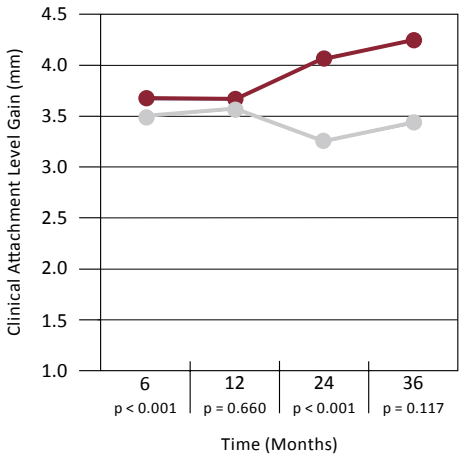
Radiographic Percent Bone Fill



Radiographic Linear Bone Growth



Clinical Attachment Level Gain

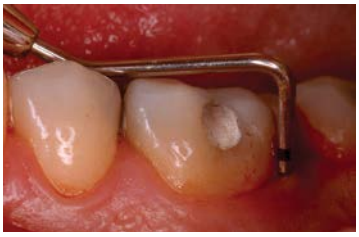


Number of patients enrolled at each time point

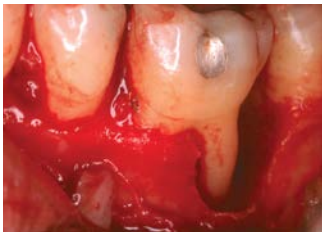
# Months	6	12	24	36
GEM 21S®	60	45	29	27
β-TCP	59	43	29	28

Representative Case from Pivotal Trial: Long-Term Follow-Up[5]

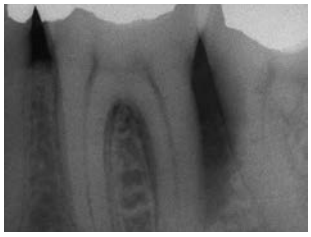
Case by Dr. Richard Kao



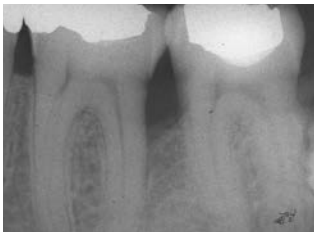
Baseline: 13 mm probing depth on the distal aspect of tooth #19



Surgical exposure revealed a 7 mm deep x 4 mm wide circumferential-2-walled intrabony defect



Baseline radiograph



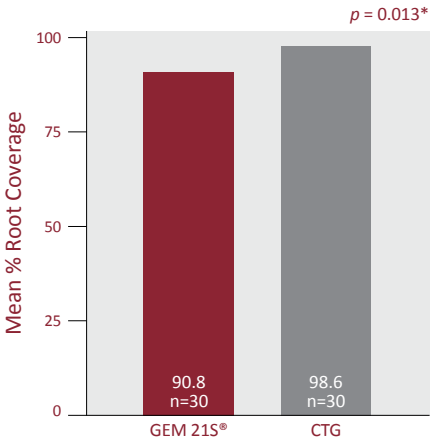
Five year post-op radiograph indicates the bony architechure and periodontal ligament space appear normal

Gingival Recession Defects

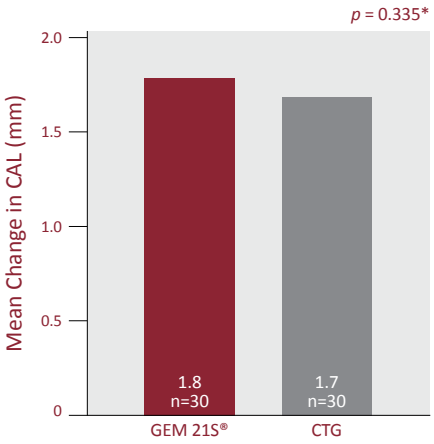
Clinical Performance

A randomized controlled clinical trial compared GEM 21S® Growth-factor Enhanced Matrix to Subepithelial Connective Tissue Grafts (CTG).* Investigators concluded that both the CTG and GEM 21S® treatments resulted in clinically significant improvements over the six month evaluation periods and were effective treatments for the correction of recession defects.[6]

Root Coverage



Clinical Attachment Level



Six Month Results

GEM 21S® treatment was statistically equivelent to CTG in the following parameters:

- Patient Satisfaction
- Esthetic Results
- Increased Keratinized Tissue

Patient Satisfaction

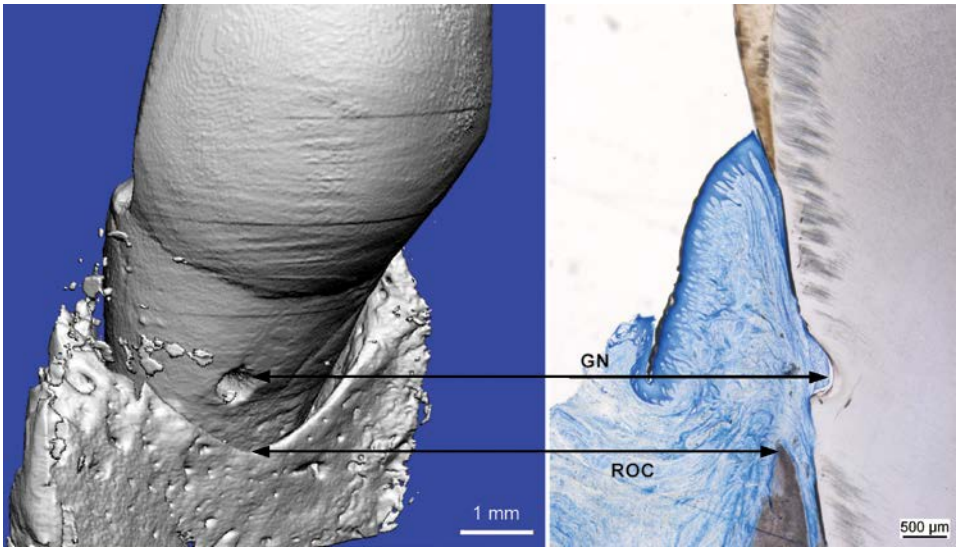
At the conclusion of the trial, patients who were in need of additional surgery unanimously stated that they would prefer treatment with GEM 21S® over a CTG because they were satisfied with the esthetic results and could avoid the harvesting of a palatal graft.

*Results obtained in this trial are based on a technique that includes methods not included in approved insert.
See Full Prescribing Information on pages 16-18.

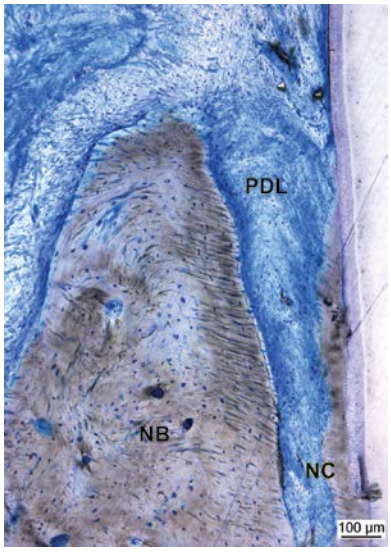
Histologic Evidence of True Periodontal Regeneration

Sites treated with *GEM 21S®* Growth-factor Enhanced Matrix consistently led to the formation of cementum with inserting connective tissue fibers and supporting alveolar bone. None of the CTG treated sites yielded evidence of periodontal regeneration.[7] *

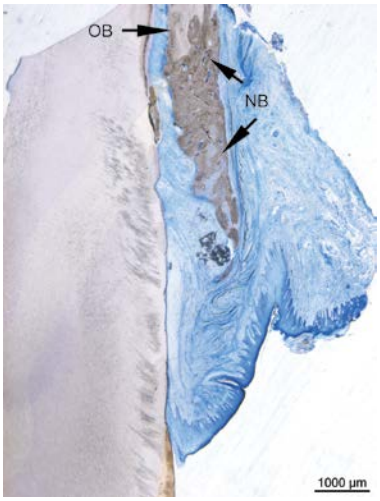
Representative case of site treated with GEM 21S®



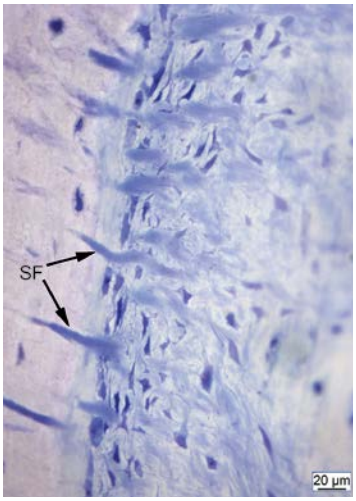
(Left) Nine months after treatment with GEM 21S®, dense cortical bone has regenerated covering the reference notch that had been placed at the presurgical osseous crest. The bone level is now just apical to the gingival reference notch (GN). ROC = regenerated osseous crest. (Right) In this ground section, both new bone and PDL have formed almost to the gingival reference notch confirming the micro CT findings

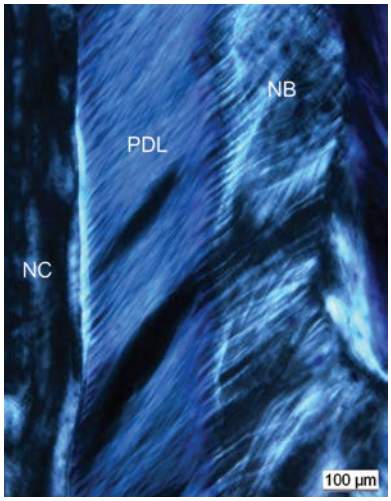


At higher power, perpendicularly oriented connective tissue fibers are seen inserting into the newly formed bone (NB) and cellular cementum (NC). PDL = periodontal ligament



In this low power image, newly formed cementum, PDL, and bone are observed 9 months after treatment with GEM 21S®. Note the clear demarcation between the old bone and the newly formed bone



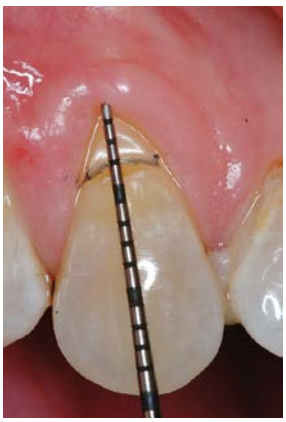


Under polarized light, Sharpey fibers (SF) are seen inserting into newly regenerated bone (NB) and cementum (NC). In the ground section, well-defined connective tissue fibers are also seen inserting into regenerated cementum. PDL = periodontal ligament[7]

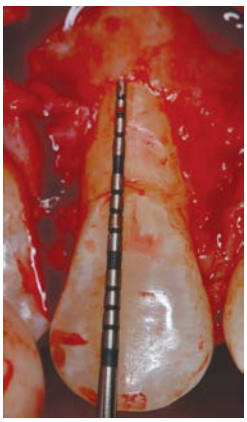
*Results obtained in this trial are based on a technique that includes methods not included in approved insert.
See Full Prescribing Information on pages 16-18.

Miller Class II Gingival Recession Defects

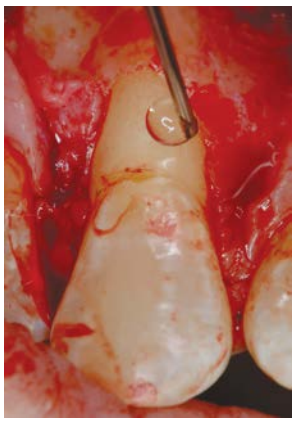
Cases by Dr. Michael McGuire



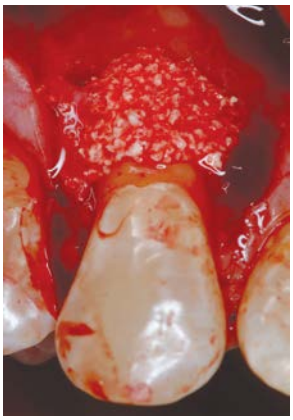
Baseline Miller Class II gingival recession defect



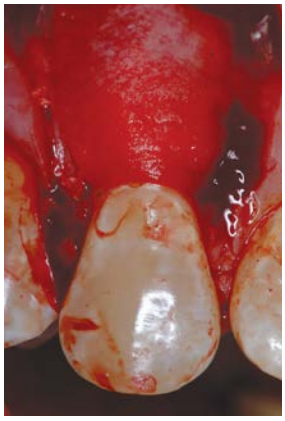
A full-thickness mucoperiosteal flap with divergent releasing incisions reveals 6 mm of labial bone loss



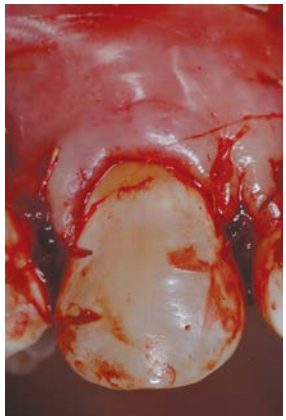
Following flap reflection and root preparation, rhPDGF-BB is placed onto the root surface*



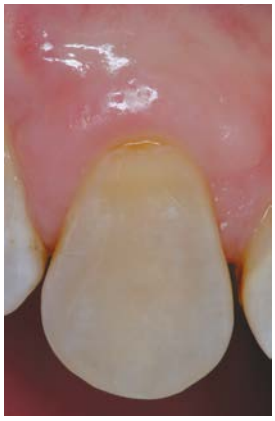
GEM 21S® is placed onto the exposed root surface no closer than 3 mm above the Cemento Enamel Junction (CEJ)



A collagen wound healing dressing is placed over the graft, partially saturated with blood and hydrated with rhPDGF-BB* and secured with resorbable sutures at each papillary position



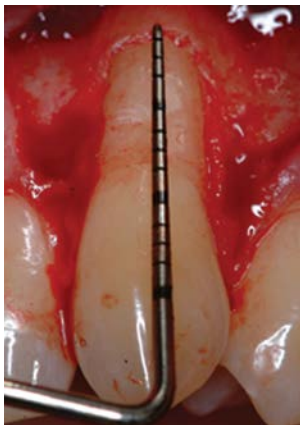
The mucoperiosteal flap is coronally repositioned to the level of the CEJ and secured with multiple interrupted sutures



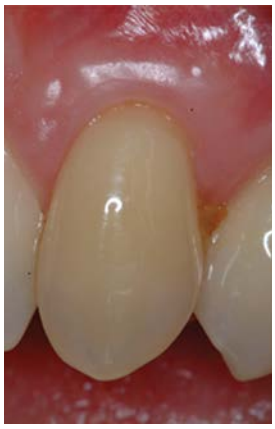
Six months post-op: the gingival margin remains at the level of the CEJ with no evidence of recession

*These steps in the procedure are not in the FDA approved GEM21S® labeling.

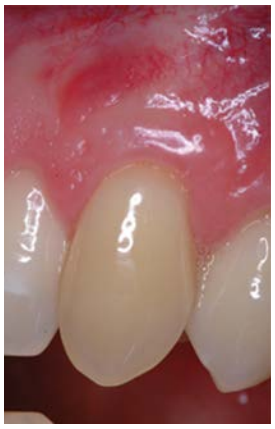
Results obtained in this trial are based on a technique that includes methods not included in approved insert. See Full Prescribing Information on pages 16-18.



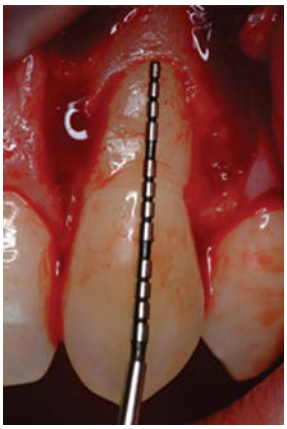
Presurgical intraoperative measurements



Soft tissue root coverage six months following surgery



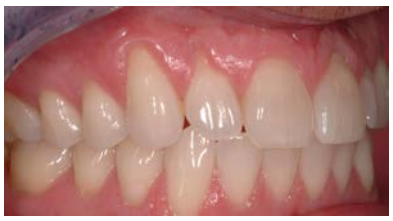
Soft tissue root coverage three years following surgery



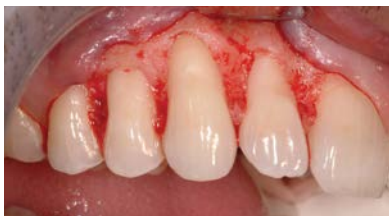
Clinical evidence of approximately 2-3 mm bone growth over previously denuded root surface at three years

Miller Class I & II Gingival Recession Defects

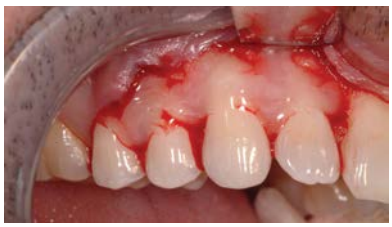
Case by Dr. Jeffrey Ganeles



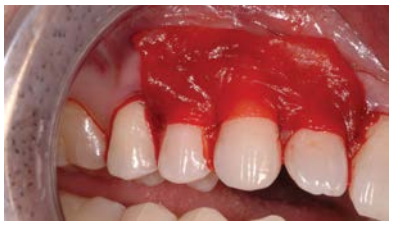
Patient presents with significant Miller Class 1 and 2 gingival recession defects on teeth numbers 5, 6 and 7. Note clefting on tooth number 7



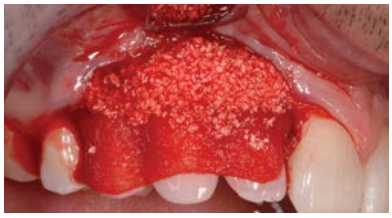
Exposed portions of the roots were debrided and root-planed using curettes and finishing burs



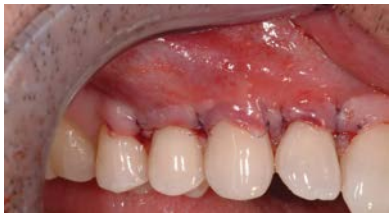
The exposed root surfaces were conditioned with EDTA for 2 minutes to remove the smear layer and then thoroughly rinsed with sterile saline



HeliTape® was properly sized and shaped, wetted with sterile saline and sutured over the exposed root surfaces using 6-0 polygalactin sutures



GEM 21S® was carefully placed to cover all exposed root surfaces and adjacent bony areas. Sufficient volume of GEM 21S® was placed in order to create space for regeneration of the attachment apparatus to occur



The flap was coronally advanced without tension coronal to the level of the CEJ of each tooth and sutured interdentally with 6-0 polygalactin sutures

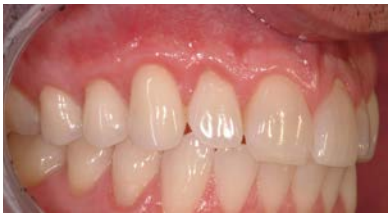
IMPORTANT SAFETY INFORMATION

GEM 21S® Growth-factor Enhanced Matrix is intended for use by periodontists/dentists/oral surgeons familiar with periodontal surgical techniques. It should not be used in the presence of untreated acute infections or untreated malignant cancerous growth at the site of use, where bone grafting is not advisable or tissue coverage is not possible and, in patients with a known hypersensitivity to one of its components. It must not be injected into your body, only placed into a defect in your teeth.

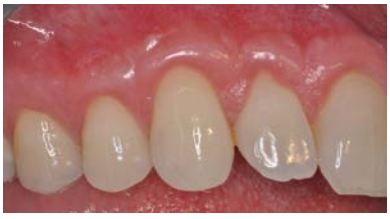
The safety and effectiveness of GEM 21S® has not been established in patients with an active malignant cancerous growth, in other non-periodontal bony locations, in patients less than 18 years old, in pregnant or nursing women, in patients with frequent/excessive tobacco use (e.g. smoking more than one pack per day) and in patients with more severe periodontal defects. In a 180 patient clinical trial, there were no serious adverse events related to GEM 21S®. Adverse events that may occur are those associated with periodontal surgical procedures in general, including swelling; pain; bleeding; dizziness; fainting; difficulty breathing; eating or speaking; sinus problems; headaches; loose teeth; infection; loss of feeling; and shock. Should any of these occur, an additional surgical procedure and/or removal of the product may be required.

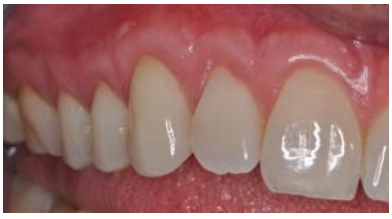
GEM 21S® contains PDGF, a protein which has been shown to promote formation of bone in periodontal defects. It is also included in REGRANEX® gel, an FDA approved product for topical treatment for diabetic ulcers in the feet and lower legs. In one study of REGRANEX® gel, an increased rate of death secondary to malignant cancer was shown with use of large amounts of the product in treatment of diabetic ulcers. Subsequent studies did not confirm that result. No relationship between use of GEM 21S® and malignant cancers or death due to malignant cancers has been shown.

See complete prescribing information on pages 16-18.



A 2-month post-operative visit demonstrates healthly gingival color and texture and maintenance of 100% root coverage

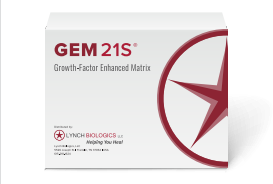




Post-operative results at 9 months demonstrate stable gingival margins and the appearance of increased tissue thickness relative to baseline. Note the increase in keratinized tissue on teeth numbers 5 and 6

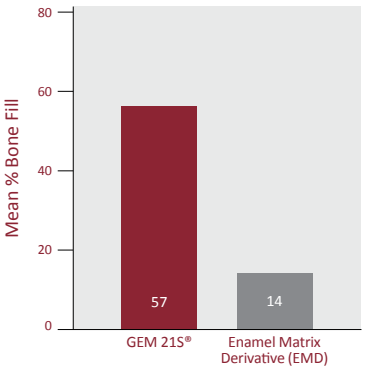
Comparison of GEM 21S® and Emdogain®

Improvements in clinical and radiographic parameters in the GEM 21S® pivotal trial compare favorably with, documented outcomes for other regenerative therapies in studies examining defects with similar baseline characteristics.[8, 9]

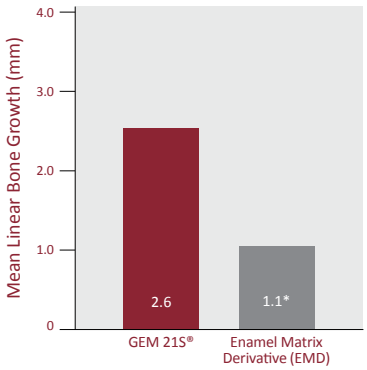
	GEM 21S®	Emdogain®
Product Description	GEM 21S® growth-factor enhanced matrix is a combination of highly purified recombinant human platelet derived growth factor-BB (rhPDGF-BB) and an osteoconductive matrix (beta-tricalcium phosphate, β-TCP). 	Emdogain® consists of a number of hydrophobic proteins that self assemble to form a matrix layer on the root surface. The primary protein is amelogenin. These proteins are delivered in a propylene glycol alginate carrier solution.[10] 
Source	Synthetic (engineered through recombinant technology)	Xenograft (porcine origin)
Amount of Growth Factor	**PDGF = 300,000 ng/ml**	**NONE**
Primary Mode of Action	Extensive in vitro and in vivo studies have demonstrated that rhPDGF-BB is a powerful stimulant of angiogenesis and significantly increases the proliferation and migration of osteoblasts and other cells of the periodontium.	Amelogenin and the other proteins in Emdogain® mediate the formation of acellular cementum on the roots of teeth and provide a matrix for tissues associated with the attachment apparatus.[10]
Radiographic Bone Fill (%)*	57% (6 months)	14% (8 months)
Radiographic Linear Bone Growth (mm)*	2.6 mm (6 months)	1.1 mm (8 months)
Clinical Attachment Level Gain*	3.7 mm (6 months)	2.7 mm (8 months)

The charts below compare the results obtained in the GEM 21S® pivotal clinical trial with two safety and efficacy studies submitted as part of the Emdogain PMA application.[8, 9, 11]

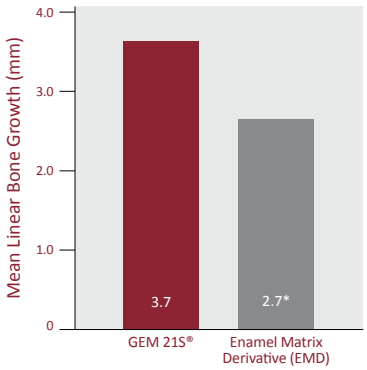
Radiographic Percent Bone Fill



Radiographic Linear Bone Growth



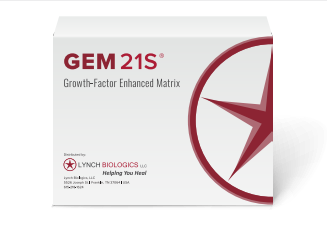
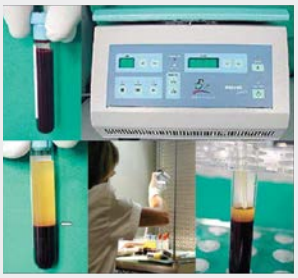
Clinical Attachment Level Gain



*GEM 21S® results at 6 months, EMD results at 8 months

Comparison of GEM 21S® and PRP or PRGF

GEM 21S® contains significantly more active growth factor than either PRP or PRGF preparations.[12, 13, 14, 15]

	GEM 21S®	Platelet Rich Plasma	Plasma Rich in Growth Factors
Product Description	GEM 21S® growth-factor enhanced matrix is a combination of highly purified recombinant human platelet derived growth factor-BB (rhPDGF-BB) and an osteoconductive matrix (beta tricalcium phosphate, β-TCP).	PRP (Platelet Rich Plasma) is a concentrated preparation of platelets sequestered from the patient's blood prepared using a specialized centrifuge technology.	PRGF (Plasma Rich in Growth Factors) is a concentrated preparation of platelets sequestered from the patient's blood prepared using a speclialized centrifuge technology.
			
Source	Synthetic (engineered through recombinant technology)	Autologous	Autologous
Blood Volume Required	NONE	20 - 60 cc	5 - 40 cc
Activation Required	NONE	Yes, Bovine Thrombin	Yes, Calcium Chloride
Contamination Risk During Preparation	Extremely Low*	Low	Fairly High
White Blood Cells Included	NO	Yes	NO
Amount of Growth Factor	**PDGF = 300,000 ng/mL** [12, 13, 14, 15]	**PDGF = 398 ng/mL** [16, 17, 18, 19]	**PDGF = 47 ng/ml** [16]

Advantages of GEM 21S® Growth-factor Enhanced Matrix

Powerful

- Contains significantly more -active growth factor than PRP or PRGF preparations [12, 13, 14, 15]

Predictable

- A well established wound healing agent that accelerates bone regeneration and soft tissue healing
- Predictable even in the most challenging cases where normal healing may be compromised

Simple to Use

- No expensive equipment to purchase and maintain
- No invasive blood drawing procedures
- No technique sensitive preparation

* When used as directed. All components/accessories are supplied sterile for single use only. The external surface of the rhPDGF-BB syringe and β-TCP cup are not sterile. Therefore, care must be taken to ensure that these components are handled in such a way that sterility is maintained in the surgical field.

Please see Full Prescribing Information on pages 16-18.

Clinical Instructions for Use

GEM 21S® Growth-factor Enhanced Matrix contains a recombinant human platelet derived growth factor (rhPDGF-BB) and a synthetic beta-tricalcium phosphate (β-TCP). Familiarization with this device and following proper surgical techniques are extremely important when using GEM 21S®.

All components are supplied sterile for single use only. The external surface of the rhPDGF-BB syringe and β-TCP cup are not sterile and therefore proper aseptic technique* should be followed when preparing GEM 21S® for use.

Remove a GEM 21S® kit from the refrigerator.

Remove tray from the carton. Inspect the components of the kit for structural integrity prior to use. If the seal of any inner or outer container is open, broken or otherwise damaged, the product must be assumed to be non-sterile and consequently must not be used.

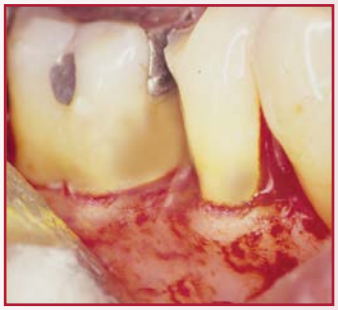
Open peel-cup lid to β-TCP container and empty contents into a sterile bowl (e.g. dappen dish) on surgical tray.

Remove syringe of rhPDGF-BB from tray and fully saturate the sterile β-TCP particles with the rhPDGF-BB solution while in the sterile surgical field.

*Reference: *Guidelines for Infection Control in Dental Health Care Settings.* Center for Disease Control. Dec. 19, 2003. MMWR, Vol 52 No. RR-17. Page 31
This information is supplementary to the GEM 21S® Full Prescribing Information provided on pages 16-18.

Using a sterile surgical instrument, gently mix to ensure all β-TCP particles are hydrated with the rhPDGF-BB solution.

Allow the product to sit for approximately ten (10) minutes before implantation to allow the growth factor to bind to the β-TCP particles.



Following exposure of the defect, all granulation tissue must be carefully removed. Thorough soft tissue debridement of the defect site is critical to successful regeneration. Granulation tissue, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.

Using a sterile surgical instrument, completely fill the defect site to the level of the surrounding bony walls with the GEM 21S® graft. Overfilling should be avoided. Use moderate pressure, taking care not to crush the particles.

Additional Considerations

To enhance the formation of new bone, GEM 21S® should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials. Primary closure should be obtained whenever possible. Any remaining product must be discarded and not reused. Pre-requisites for all regenerative procedures should include prevention of wound dehiscence, a stable clot, and minimal bacterial contamination.

Caution: Federal Law restricts this device to sale by or on the order of a dentist or physician.

DEVICE DESCRIPTION:
GEM 21S® is a completely synthetic grafting system for bone and periodontal regeneration composed of a purified recombinant growth factor and a synthetic calcium phosphate matrix.

GEM 21S® is composed of two sterile components:

- synthetic beta-tricalcium phosphate (ß-TCP) [$Ca_3 (PO_4)$] is a highly porous, resorbable osteoconductive scaffold or matrix that provides a framework for bone ingrowth, aids in preventing the collapse of the soft tissues and promotes stabilization of the blood clot. Pore diameters of the scaffold are specifically designed for bone ingrowth and range from 1 to 500 µm. The particle size ranges from 0.25 to 1.0 mm and

- highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB). PDGF is a native protein constituent of blood platelets. It is a tissue growth factor that is released at sites of injury during blood clotting. *In vitro* and animal studies have demonstrated PDGF's potent mitogenic (proliferative), angiogenic (neovascularization) and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. PDGF is known to be one protein involved in the multi-factored and complex process of bone and wound repair. Animal studies have shown PDGF to promote the regeneration of periodontal tissues including bone, cementum, and periodontal ligament (PDL).

The contents of the cup of ß-TCP are supplied sterile by gamma irradiation. Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

INDICATIONS:
GEM 21S® is indicated to treat the following periodontally related defects:
- Intrabony periodontal defects;
- Furcation periodontal defects; and
- Gingival recession associated with periodontal defects.

CONTRAINDICATIONS:
As with any periodontal procedure where bone grafting material is used, GEM 21S® is CONTRAINDICATED in the presence of one or more of the following clinical situations:

- Untreated acute infections at the surgical site;
- Untreated malignant neoplasm(s) at the surgical site;
- Patients with a known hypersensitivity to any product component (ß-TCP or rhPDGF-BB);
- Intraoperative soft tissue coverage is required for a given surgical procedure but such coverage is not possible; or
- Conditions in which general bone grafting is not advisable.

WARNINGS:
The exterior of the cup and syringe are NOT sterile. See directions for use.

It is not known if GEM 21S® interacts with other medications. The use of GEM 21S® with other drugs has not been studied. Carcinogenesis and reproductive toxicity studies have not been conducted.

The safety and effectiveness of GEM 21S® has not been established:

- In patients with an active malignant neoplasm and should therefore not be used in such patients.
- In other non-periodontal bony locations, including other tissues of the oral and craniofacial region such as bone graft sites, tooth extraction sites, bone cavities after cystectomy, and bone defects resulting from traumatic or pathological origin. GEM 21S® has also not been studied in situations where it would be augmenting autogenous bone and other bone grafting materials.
- In pregnant and nursing women. It is not known whether rhPDGF-BB is excreted in the milk of nursing women.
- In pediatric patients below the age of 18 years.
- In patients with teeth exhibiting mobility of greater than Grade II or a Class III furcation.
- In patients with frequent or excessive use of tobacco products.

Careful consideration should be given to alternative therapies prior to performing bone grafting in patients:

- Who have severe endocrine-induced bone diseases (e.g. hyperparathyroidism);
- Who are receiving immunosuppressive therapy; or
- Who have known conditions that may lead to bleeding complications (e.g. hemophilia).

The GEM 21S® grafting material is intended to be placed into periodontally related defects. It must not be injected systemically.

The radiopacity of GEM 21S® is comparable to that of bone and diminishes as GEM 21S® is resorbed. The radiopacity of GEM 21S® must be considered when evaluating radiographs as it may mask underlying pathological conditions.

PRECAUTIONS:
GEM 21S® contains becaplermin – a recombinantly produced, human platelet-derived growth factor, homodimer BB (rhPDGF-BB), which is a protein that has been shown to promote the formation of bone in periodontal defects. rhPDGF-BB ("PDGF") is also the active ingredient of another FDA approved product, REGRANEX® Gel, which is a topical gel formulation, indicated for the treatment of lower extremity diabetic neuropathic ulcers.[1]

An increased rate of mortality secondary to malignancy with use of high quantities (i.e., 3 or more tubes of REGRANEX® Gel) was demonstrated in a single study of its use in treatment of diabetic, neuropathic ulcers. Two subsequent studies did not demonstrate this increased rate. No relationship has been demonstrated regarding use of PDGF in periodontal defects and malignancy or mortality secondary to malignancy. Note the following information:

Post-Approval Studies regarding Cancer Risk in Patients Treated with REGRANEX® Gel and Their Applicability to use of GEM 21S®.

The product label of REGRANEX® Gel contains a warning identifying an increased rate of mortality secondary to malignancy in patients treated with three or more tubes of this product based on the results of the first of three post-approval studies of REGRANEX® Gel.

Summary of the Three REGRANEX® Post-Approval Studies' Findings Regarding Cancer

First, in a retrospective study[2] of a medical claims database, cancer rates and overall cancer mortality were compared between 1622 patients who used REGRANEX® Gel and 2809 matched comparators. Estimates of the incidence rates reported below may be under-reported due to limited follow-up for each individual.

- The incidence rate for all cancers was 10.2 per 1000 years for patients treated with REGRANEX® Gel and 9.1 per 1000 years for the comparators. Adjusted for several possible confounders, the rate ratio was 1.2 (95% confidence interval 0.7-1.9). Types of cancers varied and were remote from the site of treatment.
- The incidence rate for mortality from all cancers was 1.6 per 1000 person years for those who received REGRANEX® Gel and 0.9 per 1000 person years for the comparators. The adjusted rate ratio was 1.8 (95% confidence interval 0.7-4.9).
- The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGRANEX® Gel was 3.9 per 1000 years and 0.9 per 1000 person years for the comparators. The rate ratio for cancer mortality among those who received 3 or more tubes relative to those who received none was 5.2 (95% confidence interval 1.6-17.6), although this estimate ignored confounders in the incidence model due to the small number of events in this group.

These results are based on follow-up information, post-treatment out to 3 years. The information indicates that patients treated with REGRANEX® Gel did not have a greater incidence of post-treatment cancer, but patients treated with 3 or more tubes of REGRANEX® Gel had a statistically significant increased rate of mortality, i.e., a 5.2 fold greater rate, secondary to malignancy, unadjusted for other confounders. The malignancies observed were distant from the site of application in becaplermin (PDGF) users evaluated in the postmarketing study.

Second, in the follow-up epidemiologic study of these same patient cohorts (post-treatment years 3 to 6), investigators found that the becaplermin treated group receiving 3 or more tubes of REGRANEX® Gel did not have an increased incidence of cancer as compared to the control group. While the cancer mortality rate remained higher (the adjusted rate ratio was 2.4 with 95% confidence interval 0.8-7.4) in the becaplermin treated group receiving 3 or more tubes of REGRANEX® Gel, the rate was not statistically different than the rate of cancer mortality of the control group during this observation period. The findings of the second study of patients in post-treatment years 4 to 6 are not considered to negate the findings of the first study of patients in post-treatment years 1 to 3, just as the findings of the first study are not considered to negate the findings of the second study.

Third, a study evaluating cancer risk associated with the use of Becaplermin (rhPDGFBB) for the treatment of diabetic foot ulcers was conducted by the Veterans Administration. This study compared cancer rates and overall cancer mortality between 6429 patients who used REGRANEX® Gel and 6429 matched comparators followed over 11 years (1998 through 2009). The hazard ratio for cancer mortality among those who received 3 or more tubes of REGRANEX® Gel relative to those who received none was 1.04 (95% confidence interval 0.73-1.48). This study provided no evidence of a cancer risk among becaplermin users, and did not indicate an elevated risk of cancer mortality.

These three studies have limited relevance to the use of GEM 21S® in treatment of periodontal defects due to:

- higher doses of rhPDGF-BB with REGRANEX® Gel compared to GEM 21S®,
- their different intended uses,
- the locations where the products containing PDGF were placed,
- possible gender bias, and
- limited statistical power to detect small incident cancer death risks.

Non-clinical Toxicology Carcinogenesis, Mutagenesis, Impairment of Fertility Testing
Becaplermin was not genotoxic in a battery of *in vitro* assays (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair) in reports identified for the REGRANEX® Gel product, nor was becaplermin found to be mutagenic in mutagenicity evaluations conducted for GEM 21S®. Becaplermin/REGRANEX® Gel was also not mutagenic in an *in vivo* assay for the induction of micronuclei in mouse bone marrow cells. Other non-clinical studies including long term implantation, acute and repeated dose toxicity, reproductive/development toxicity, and rodent pharmacokinetic studies were conducted to evaluate the safety of rhPDGF-BB at doses far in excess of the usual dental dose of a single administration in GEM 21S®. These studies have shown no adverse findings.

No Clinical Evidence of Increased Cancer Incidence or Mortality in GEM 21S® Patients

There is no information that suggests an increased cancer incidence or mortality associated with PDGF in data from human clinical trials of GEM 21S® or in preclinical studies of PDGF. Additionally, no potential safety concerns related to cancer or cancer mortality have been identified through routine postmarketing pharmacovigilance; however, it is important to recognize that the pharmacovigilance mechanism is a voluntary system in which patient outcomes are not actively researched.

This information is being supplied to permit the attending surgeon to evaluate all known aspects of the use of GEM 21S® in his/her intended patients. Interpretation of the results of these and all studies should be made with caution. Use of the product should be evaluated with this is precautionary information in mind.

GEM 21S® is intended for use by clinicians familiar with periodontal surgical grafting techniques.

GEM 21S® is supplied in a single use kit. Any unopened unused material must be discarded and components of this system should not be used separately.

HOW GEM 21S® IS SUPPLIED:
Each GEM 21S® kit consists of:

(1) one cup containing 0.5 cc of ß-TCP particles (0.25 to 1.0 mm); and
(2) one syringe containing a solution of 0.5 mL rhPDGF-BB (0.3 mg/mL).

All of these components are for single use only.

CLINICAL STUDY:
A 180 patient, double-blinded, controlled, prospective, randomized, parallel designed multicenter clinical trial in subjects who required surgical intervention to treat intraosseous periodontal defects was completed.

The major inclusion criteria were:
a. No localized aggressive periodontitis
b. Treatment site with the following characteristics:
   - Probing pocket depth ≥ 7 mm at baseline,
   - After surgical debridement, ≥ 4 mm vertical bone defect with at least 1 bony wall,
   - Sufficient keratinized tissue to allow complete tissue coverage of defect, and
   - Radiographic base of defect ≥ 3 mm coronal to the apex of the tooth.

The major exclusion criteria were:
a. No periodontal surgery on the subject tooth within the last year.
b. No significant recent tobacco use.
c. Allergy to yeast-derived products.
d. Using an investigational therapy within the past 30 days.

The duration of the study was six (6) months following implantation of the product. Patients were randomized into three patient treatment groups:

- Group I (n=60): ß-TCP and 0.3 mg/mL rhPDGF-BB (GEM 21S®)
- Group II (n=61): ß-TCP and 1.0 mg/mL rhPDGF-BB
- Group III (n=59): ß-TCP and buffer alone (active control)

The baseline characteristics among the subjects in each group were similar with the exception of "base of defect to root apex." Group I had a mean defect which was significantly less than in Group III (6.5 mm vs. 7.7 mm, p = 0.04).

Schedule of Patient Visits
Patients had 4 visits over the 6 months prior to surgery and device implantation. Scaling and root planing were performed if necessary within 3 months prior to the implant surgery date (Visit 5). Following implantation, subjects underwent 4 follow-up visits during the first 24 days to assess wound healing and pain assessment and then 4 further follow-up visits every 6 weeks through 6 months. At these latter visits, clinical measurements and radiographs were performed.

Endpoints
The pre-defined primary effectiveness endpoint was the mean change in CAL between baseline and 6 months. Results were to be compared 1) for each group to a historically established level of effectiveness (mean change of 1.5 mm) and 2) between Group I and Group III. The pre-defined secondary endpoints included:

- Comparison of linear bone growth (LBG)
- Comparison of % bone defect fill (%BF) based on radiographs
- Area under the curve for change in CAL
- Change in CAL between baseline and 6 months
- Pocket depth reduction (PDR) change between baseline and 6 months
- Gingival recession (GR) change between baseline and 6 months
- Wound healing during first 3 weeks post-operatively

Primary Endpoint Results
The primary effectiveness endpoint was evaluated using the mean change in CAL gain (mm) from baseline to 6 months for each of the three groups. Mean changes at 6 months are presented in the Table below:

Group of Interest and Change	Control Group and Change	Difference	p-value
Group I 3.7 mm	Historical 1.5 mm	2.2 mm	< 0.001
Group II 3.7 mm	Historical 1.5 mm	2.2 mm	< 0.001
Group III 3.5 mm	Historical 1.5 mm	2.0 mm	< 0.001
Group I 3.7 mm	Group III 3.5 mm	0.2 mm	0.20

As seen in the table above, all three groups, including the control group, had statistically and clinically meaningful mean CAL gains when compared to the historically established 1.5 mm level (p < 0.001). At 6 months, there was no statistically or clinically significant difference in CAL gain for the low-concentration group (Group I) when compared to the active control without GEM 21S® (p = 0.20). However, at 3 months (not included in the Table above), the difference was 0.5 mm (3.8 mm vs. 3.3 mm) which was statistically significant (p = 0.04) suggesting that the device may facilitate earlier resolution of periodontal intrabony lesions.

Secondary Endpoint Results
As noted above, numerous secondary endpoints were pre-defined in the clinical protocol. The results for these are presented in the Table below. The results represent changes from baseline to 6 months unless otherwise noted.

Parameter	Primary Group and Mean Change	Control Group and Mean Change	Difference in Means	p-value
Linear Bone Growth	Group I 2.52 mm	Group III 0.89 mm	1.63 mm	< 0.001
	Group II 1.53 mm	Group III 0.89 mm	0.64 mm	0.02
% Bone Fill	Group I 56.0%	Group III 17.9%	38.1%	< 0.001
	Group II 33.9%	Group III 17.9%	16.0%	0.02
AUC for CAL Gain (mm-weeks)	Group I 67.5	Group III 60.1	7.4	0.05
	Group II 61.8	Group III 60.1	1.7	0.35
CAL Gain	Group II 3.7 mm	Group III 3.5 mm	0.2 mm	0.29
PDR	Group I 4.4 mm	Group III 4.2 mm	0.2 mm	0.38
	Group II 4.3 mm	Group III 4.2 mm	0.1 mm	0.66
PDR - 3 Months*	Group I 4.2 mm	Group III 4.2 mm	0.0 mm	0.80
	Group II 4.1 mm	Group III 4.2 mm	0.1 mm	0.67
GR	Group I 0.7 mm	Group III 0.7 mm	0.0 mm	0.95
	Group II 0.6 mm	Group III 0.7 mm	0.1 mm	0.81
GR - 3 Months*	Group I 0.5 mm	Group III 0.9 mm	0.4 mm	0.04
	Group II 0.7 mm	Group III 0.9 mm	0.2 mm	0.46

* Not a pre-defined secondary or primary endpoint.

The table illustrates that both the low- and high-dose device achieved significant improvement over the control device (no rhPDGF-BB) at 6 months for linear bone growth and percent bone fill. Although other parameters (CAL gain and gingival recession) showed significant changes at 3 months for the low-dose group, these benefits were not maintained over control at 6 months. Again, several of these results suggest that the device facilitates earlier resolution of periodontal intrabony lesions.

Long-Term Follow-up
Throughout the 24 month observation period, study data demonstrated the continued long-term efficacy of GEM 21S® treatment.

Radiographic (x-ray) analysis of bone growth showed that over the 24 month observation period, all treatment groups demonstrated an increase in bone fill. At the end of the 24 month observation period, the GEM 21S® group demonstrated a statistically significant greater amount of bone formation compared to the ß-TCP matrix alone. In addition, after 24 months, the ß-TCP group failed to experience the level of radiographic bone fill that was achieved by the GEM 21S® group at the end of the first six months of this trial.

Long-Term Parameter	Primary Group and Mean Change	Control Group and Mean Change	Difference in Means	p-value
Linear Bone Growth - 24 Months	Group I 3.32 mm	Group III 1.81 mm	1.51 mm	< 0.001
	Group II 2.40 mm	Group III 1.81 mm	0.59 mm	0.074
% Bone Fill - 24 Months	Group I 68.3%	Group III 41.5%	26.8%	< 0.001
	Group II 57.3%	Group III 41.5%	15.8%	0.022
CAL Gain - 24 Months	Group I 4.07 mm	Group III 3.28 mm	0.79 mm	0.117
	Group II 3.47 mm	Group III 3.28 mm	0.19 mm	0.711
PDR - 24 Months	Group I 4.48 mm	Group III 3.79 mm	0.69 mm	0.121
	Group II 4.03 mm	Group III 3.79 mm	0.24 mm	0.597
Change in GR - 24 Months	Group I 0.41 mm	Group III 0.52 mm	0.11 mm	0.726
	Group II 0.57 mm	Group III 0.52 mm	-0.05 mm	0.850

Comparison of Emdogain® and GEM 21S® Pivotal Clinical Trial Results
The table below compares the results obtained in the GEM 21S® pivotal clinical trial to two safety and efficacy studies submitted as part of the Emdogain® PMA application. Improvements in clinical and radiographic parameters in the GEM 21S® trial compare favorably with, or exceed, documented outcomes for other regenerative therapies in studies examining defects with similar baseline characteristics.

	Baseline Measures			Treatment Outcomes		
	Probing Pocket Depth (mm)	Clinical Attachment Level (mm)	Defect Depth (mm)	Clinical Attachment Level Gain (mm)	Radiographic Linear Fill (mm)	Radiographic % Defect Fill
GEM 21S® N=60	8.6 ± 1.6	9.1 ± 1.6	6.0 ± 1.6	3.7 ± 1.6	2.5 ± 1.6	56
Emdogain®* N=34	7.8 ± 1.1	9.4 ± 1.5	7.1 ± 2.2	2.1 ± 1.5	0.9 ± 0.6	13
Emdogain® N=104**	7.4 ± 1.2	8.7 ± 1.7	N/A	3.1 ± 1.4	1.2 ± 1.1	15

Emdogain is a registered trademark of Bioventures BV Corporation (PMA# P930021).
*Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontol.* 1997;24:705-714.
**Zetterstrom O, Andersson C, Eriksson L et al. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. *J Clin Periodontol.* 1997;24:697-704.

Safety
During the initial 6 month observation period, there were 18 patients (7 Group I, 6 Group II, 5 Group III) with adverse events reported as related to the device. None of these were serious. They were all classified as surgical site reactions. There were no significant differences in the incidence of adverse events across the three treatment groups.
No safety measurements were collected during the long term follow-up observation period (month 7 through 24).

Conclusion
GEM 21S® was shown, by both clinical and radiographic measures, to be effective in treating moderate to severe periodontally related defects within six months of implantation. The therapeutic effects of GEM 21S® compare favorably with, or exceed, documented outcomes with enamel matrix derivative. When implanted into bony defects of the periodontium, GEM 21S® has been shown to speed clinical attachment level (CAL) gain, reduce gingival recession, and improve bone growth resulting in increased bone fill of the osseous defect. The long-term follow up data demonstrates that the effectiveness of GEM 21S® is sustained for at least 2 years and remains statistically significantly superior to the control group in terms of radiographic percent bone fill and linear bone gain.

ADVERSE EVENTS:
Although no serious adverse reactions attributable to GEM 21S® were reported in a 180 patient clinical trial, patients being treated with GEM 21S® may experience any of the following adverse events that have been reported in the literature with regard to periodontal surgical grafting procedures: swelling; pain; bleeding; hematoma; dizziness; fainting; difficulty breathing, eating, or speaking; sinusitis; headaches; increased tooth mobility; superficial or deep wound infection; cellulitis; wound dehiscence; neuralgia and loss of sensation locally and peripherally; and, anaphylaxis.

Occurrence of one or more of these conditions may require an additional surgical procedure and may also require removal of the grafting material.

DIRECTIONS FOR USE:
ASEPTIC TECHNIQUE
- The contents of the cup of ß-TCP are supplied sterile by gamma radiation.
- Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

The exterior portion of the cup of ß-TCP and the exterior surface of the syringe are non-sterile. Because of this, it is recommended that transfer of the ß-TCP particles to a sterile container in the sterile operating field be performed in a sterile manner prior to adding the PDGF from the syringe. Care must also be taken to minimize crushing the ß-TCP particles. Appropriate sterile transfer techniques must be used to prevent contamination of the contents of the cup and syringe.

SURGICAL TECHNIQUE
Familiarization with the device and following proper surgical grafting techniques are extremely important when using GEM 21S®. Radiographic evaluation of the defect site prior to use is essential to accurately assess the extent of the defect and to aid in the placement of the grafting material.

Following exposure of the defect with a full thickness mucoperiosteal flap, all granulation tissue must be carefully removed. Thorough soft tissue debridement of the defect is critical to successful regeneration. Granulation tissue, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.

Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of GEM 21S® needed to fill the defect. For best results, GEM 21S® must completely fill the defect to the level of the surrounding bony walls. Overfilling should be avoided. The clinician prepares the GEM 21S® graft by fully saturating the ß-TCP particles with the rhPDGF-BB solution and letting the product sit for approximately ten (10) minutes. Proper aseptic technique must be employed in preparing and applying GEM 21S®.

The saturated GEM 21S® should be placed into the defect using moderate pressure, taking care not to crush the particles. In order to enhance the formation of new bone, GEM 21S® should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials. Following placement of the GEM 21S® and completion of any additional surgical steps, the mucoperiosteal flaps should be sutured to achieve primary closure wherever possible.

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable clot and minimal bacterial contamination.

The GEM 21S® kit and its components must not be re-sterilized by any method or reused. Inspect each individual sterile component of the kit for structural integrity prior to use. If the seal of any inner or outer container is open, broken or otherwise damaged, the product must be assumed to be non-sterile and consequently, must not be used.

Any opened unused material must be discarded and components of this system should not be used separately.

STORAGE CONDITIONS:
The GEM 21S® kit must be refrigerated at 2°-8° C (36°-46° F). Do not freeze. The individual rhPDGF-BB component must be refrigerated at 2°-8° C (36°-46° F). The ß-TCP cup can be stored at room temperature, up to 30° C (86° F). The rhPDGF-BB component must be protected from light prior to use; do not remove from outer covering prior to use.

Do not use after the expiration date.

BIOCOMPATIBILITY:
GEM 21S® biocompatibility has been demonstrated in accordance with the International Standard ISO 10993-1:1997 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing."

[1] **Comparison of GEM 21S® and REGRANEX® Gel**
The clinical evaluation of REGRANEX® Gel included a treatment regimen of applying the gel daily to skin ulcers for up to 20 weeks. Patients who were observed in the first study to have the unadjusted 5.2-fold greater rate of mortality due secondarily to cancer would have received 450 mg, or more, of PDGF. Each tube of REGRANEX® Gel contains 15 g of a 0.01% formulation of PDGF.

Patients treated with GEM 21S®, on a one-time basis could receive 150 µg of PDGF since each GEM 21S® kit contains 0.5 mL of a 0.3 mg PDGF formulation. Patients who have periodontal defects may have periodontal disease and could require multiple defect repairs and therefore, per the treating physician's opinion for the use of GEM 21S®, patients may be treated with more than the one-time amount of 150 µg PDGF.

The amount of PDGF in GEM 21S® used in repair of 1 periodontal defect is 3000 fold less than the amount of PDGF in three tubes of REGRANEX® Gel. There are many variables specific to the REGRANEX® Gel patient population which might influence the apparent PDGF-mortality rate association. Not least among these variables is the fact that patients with known malignancies were allowed to be treated with REGRANEX® Gel whereas physicians are instructed not to treat patients with GEM 21S® who have active neoplasms.

[2] Bench and Clinical Data Regarding GEM 21S® Do Not Indicate an Increased Cancer Incidence or Mortality.

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References

1. Wang HL, Pappert TD. Castelli WA, Chiego DJ Jr., Shyr Y, Smith BA, The Effect of Platelet-Derived Growth Factor on the Cellular Response of the Periodontium: An Autogradiographic Study on Dogs. *J Periodontal.* 1994 May; 65 (5): 429-36.
2. Graves DT. The Use of Biologic Response Modifiers in Human Clinical Trials. *Ann Periodontol.* 1997; 2: 259-267.
3. Piche JE, Graves DT. Study of the Growth Factor Requirements of Human Bone-Derived Cells: a Comparison with Human Fibroblasts. *Bone.* 1989; 10(2): 131-189.
4. PMA #040013: Data on file, Luitpold Pharmaceuticals, Inc.
5. Richard T. Kao and Samuel E. Lynch. Stability of Recombinant Human Platelet-Derived Growth Factor-BB—Regenerated Periodontal Defects: Sixty-Month Clinical and Radiographic Observations. *Clinical Advances In Periodontics.* 2011; 1:132-141.
6. Michael K. McGuire, E. Todd Scheyer, and Peter Schupbach. Growth Factor-Mediated Treatment of Recession defects: A Randomized Controlled Trial and Histologic and Microcomputed Tomography Examination. *J Periodontal.* 2009; 80(4): 550-564.
7. McGuire MK, Scheyer ET, Nevins M, Schupbach P. Evaluation of a Human Recession Defects Treated with Coronally Advanced Flaps and Either Purified Recombinant Human Platelet-Derived Growth Factor-BB with Beta Triacalcium Phosphate or Connective Tissue: A Histologic and Microcomputed Tomographic Examination. *Int J Periodontics Restorative Dent.* 2009; 29:7-21.
8. Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontol.* 1997;24:705-714.
9. Zetterstrom O, Andersson C, Driksson L et al. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. *J Clin Periodontol.* 1997;24:697-704.
10. www.straumann.us.
11. Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, McAllister BS, Murphy KS, McClain PK, Nevins ML, Paquette DW, Han TJ, Reddy MS, Lavin PT, Genco RJ, Lynch SE. Platelet Derived Growth Factor (rhPDGF-BB) Stimulates Bone Fill and Rate of Attachment Level Gain. Results of a Large Multicenter Randomized Controlled Trial. *J Periodontol.*, 2005; 76: 2205-2215.
12. Bowen-Pope DF, Malpass TW, Foster DM, Ross R. Platelet-derived growth factor in vivo: Levels, activity, and rate of clearance. *Blood.* 1984; 64:458-469.
13. Huang JS, Huang SS, Deuel TF. Human platelet-derived growth factor: Radioimmunoassay and discovery of a specific plasma-binding protein. *J Cell Biol.* 1983; 97:383-388.
14. Singh JPK, Chailkin MA, Stiles CD. Phylogenetic analysis of platelet-derived growth factor by radio-receptor assay. *J Cell Biol.* 1982; 95:667-671.
15. www.harvesttech.com/harvest-prp-performance
16. Weibrich G, Kleis w, et al. Comparison of the Platelet Concentrate Collection System with the Plasma-Rich-in-Growth-Factors Kit to Produce Platelet-Rich Plasma: A Technical Report. *Int J Oral Maxillofac Implants.* 2005; 20:118-123.
17. Performance characteristics for the Smart Prep 2 APC collection system. Harvest Technology.
18. Weibrich G et al., The harvest Smart PRePTM system versus the Friadent-Schutze platelet-rich plasma kit. *Clin Oral Implants.* Res 2003 14: 233-239.
19. Weibrich JG, Kleis WK, Hafner G. Growth factor levels in the platelet-rich plasma produced by 2 different methods: curasan-type PRP kit versus PCCS PRP system. *Int J Oral Maxillofac Implants.* 2002 17: 184-190.

IMPORTANT SAFETY INFORMATION

GEM 21S® Growth-factor Enhanced Matrix is intended for use by periodontists/dentists/oral surgeons familiar with periodontal surgical techniques. It should not be used in the presence of untreated acute infections or untreated malignant cancerous growth at the site of use, where bone grafting is not advisable or tissue coverage is not possible and, in patients with a known hypersensitivity to one of its components. It must not be injected into your body, only placed into a defect in your teeth.

The safety and effectiveness of GEM 21S® has not been established in patients with an active malignant cancerous growth, in other non-periodontal bony locations, in patients less than 18 years old, in pregnant or nursing women, in patients with frequent/excessive tobacco use (e.g. smoking more than one pack per day) and in patients with more severe periodontal defects. In a 180 patient clinical trial, there were no serious adverse events related to GEM 21S®. Adverse events that may occur are those associated with periodontal surgical procedures in general, including swelling; pain; bleeding; dizziness; fainting; difficulty breathing; eating or speaking; sinus problems; headaches; loose teeth; infection; loss of feeling; and shock. Should any of these occur, an additional surgical procedure and/or removal of the product may be required.

GEM 21S® contains PDGF, a protein which has been shown to promote formation of bone in periodontal defects. It is also included in REGRANEX® gel, an FDA approved product for topical treatment for diabetic ulcers in the feet and lower legs. In one study of REGRANEX® gel, an increased rate of death secondary to malignant cancer was shown with use of large amounts of the product in treatment of diabetic ulcers. Subsequent studies did not confirm that result. No relationship between use of GEM 21S® and malignant cancers or death due to malignant cancers has been shown.

See complete prescribing information on pages 16-18.

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