Straumann® Emdogain® Application In Conjunction With Minimally Invasive Surgical Technique For Periodontal Disease Treatment: A Split-Mouth Design Study

CR 01/15

Date: 29 Mar 2018 Version 5.0

Protocol reviewed and approved by:

Disha Jelani
Clinical Study Manager
Signature
Date: 09 Apr 2018

Sarah Hackett
Senior Manager, Clinical Research
Signature
Date: 09 Apr 2018

Michel Mallaun, PhD
Head of Clinical Operations
Signature
Date: 10 Apr 2018

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# Contact Information

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Veronique Benhamou, DDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinique par excellence</td>
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<tr>
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<td>1155 Robert Bourassa</td>
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<tr>
<td></td>
<td>Montreal, QC H3B 3A7</td>
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<td>Canada</td>
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<td></td>
<td>Email: <a href="mailto:veronique.benhamou@mcgill.ca">veronique.benhamou@mcgill.ca</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Jennifer Hirsch Doobrow, DMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Periodontal &amp; Implant Associated, Inc.</td>
</tr>
<tr>
<td></td>
<td>315 Second Street SE</td>
</tr>
<tr>
<td></td>
<td>Cullman, AL 35055</td>
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<tr>
<td></td>
<td>USA</td>
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<tr>
<td></td>
<td>Phone +1 256 734 8588</td>
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<tr>
<td></td>
<td>Email: <a href="mailto:doobrowdmd@hotmail.com">doobrowdmd@hotmail.com</a></td>
</tr>
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<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Pamela K. McClain, DDS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Periodontics</td>
</tr>
<tr>
<td></td>
<td>11200 E Mississippi Ave</td>
</tr>
<tr>
<td></td>
<td>Aurora, CO 80012-3202</td>
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<tr>
<td></td>
<td>USA</td>
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<tr>
<td></td>
<td>Phone +1 303 695 7885</td>
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<tr>
<td></td>
<td>Email: <a href="mailto:periopam@aol.com">periopam@aol.com</a></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Prof. Dr. Dr. h.c. Adrian Kasaj, M.Sc</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Universitätsmedizin der Johannes</td>
</tr>
<tr>
<td></td>
<td>Gutenberg Universität Mainz</td>
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<td></td>
<td>Poliklinik für Zahnerhaltungskunde</td>
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<tr>
<td></td>
<td>Augustusplatz 2</td>
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<td></td>
<td>Tel: 06131 177157</td>
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<td></td>
<td>55131 Mainz</td>
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<td></td>
<td>Germany</td>
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<td></td>
<td><a href="mailto:adrian.kasaj@unimedizin-mainz.de">adrian.kasaj@unimedizin-mainz.de</a></td>
</tr>
</tbody>
</table>
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|         | CH- 4002 Basel  
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| Study Manager: | Evelyne Buehler  
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<table>
<thead>
<tr>
<th>Head of Clinical Operations:</th>
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<tbody>
<tr>
<td>Michel Mallaun, PhD</td>
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<tr>
<td>Institut Straumann AG</td>
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<tr>
<td>Peter Merian Weg 12</td>
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<tr>
<td>CH- 4052 Basel</td>
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<td>Switzerland</td>
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<td>Phone: +41 61 965 14 23</td>
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<td>Fax: +41 61 965 11 10</td>
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<tr>
<td>Email: <a href="mailto:michel.mallaun@straumann.com">michel.mallaun@straumann.com</a></td>
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<td>CH- 4002 Basel</td>
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<tr>
<td>Switzerland</td>
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<tr>
<td>Phone: +41 61 965 1312</td>
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<tr>
<td>Fax: +41 61 965 1120</td>
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<tr>
<td>Email: <a href="mailto:evelyn.buehler@straumann.com">evelyn.buehler@straumann.com</a></td>
</tr>
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</table>
Abbreviations

ADE    Adverse Device Effect
AE     Adverse Event
ASADE  Anticipated Serious Adverse Device Effect
BoP    Bleeding on Probing
CAL    Clinical Attachment Level
CBCT   Cone Beam Computed Tomography
CE     Conformité Européenne
CEJ    Cemento-Enamel Junction
CFR    Code of Federal Regulations
CRF    Case Report Form
DD     Device Deficiencies
DMP    Data Management Plan
EDTA   Ethylenediaminetetraacetic acid, Edetic acid
FDA    Food and Drug Administration
FMPS   Full Mouth Plaque Score
GCP    Good Clinical Practice
GM     Gingival Margin
ICF    Informed Consent Form
ICH    International Conference on Harmonization
IFU    Instructions For Use
IRB    Institutional Review Board
ISO    International Organization for Standardization
ml     Milliliter
mm     Millimeter
MP     Monitoring Plan
PPD     Probing Pocket Depth
SADE    Serious Adverse Device Effect
SAE     Serious Adverse Event
SAP     Statistical Analysis Plan
SOP     Standard Operating Procedures
SRP     Scaling and Root Planing
USADE   Unanticipated Serious Adverse Device Effect
VAS     Visual Analog Scale

Note:
- The term Emdogain® used throughout this document refers to the following device:
  Straumann® Emdogain®
- The term PrefGel® used throughout this document refers to the following device:
  Straumann® PrefGel®
## Synopsis

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Straumann® Emdogain® Application In Conjunction With Minimally Invasive Surgical Technique For Periodontal Disease Treatment: A Split-Mouth Design</th>
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<tbody>
<tr>
<td>Study Protocol Number</td>
<td>CR 01/15</td>
</tr>
<tr>
<td>Study Registration</td>
<td>This protocol will be registered at clinicaltrials.gov before enrollment begins.</td>
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**Objectives**

The aim of this controlled study is to assess the clinical outcomes and patient reported outcomes of using minimally invasive surgical procedure with Straumann® Emdogain® as an adjunct (test treatment) or without Straumann® Emdogain® (control treatment).

- **Primary Objective:** To evaluate the regenerative potential of Straumann® Emdogain® by looking at differences in Clinical Attachment Level (CAL) between the test and control treatments.

- **Secondary Objective:** To evaluate the regenerative potential of Straumann® Emdogain® by looking at differences in:
  - Gingival Margin (GM)
  - Probing Pocket Depth (PPD)
  - Full Mouth Plaque Score (FMPS)
  - Bleeding on Probing (BoP)
  - Post-surgical pain,
  - Root dentin hypersensitivity

between the test and control treatments.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Post-market, prospective, split-mouth, controlled, multi-center study.</th>
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</thead>
<tbody>
<tr>
<td>Study Population</td>
<td>The study population will consist of subjects aged 18 to 85 with moderate to severe chronic, generalized periodontitis with pockets of 5 mm – 8 mm probing depth in at least 2 pockets per contralateral quadrants in one arch.</td>
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</tbody>
</table>

**Inclusion Criteria**

- Subjects must have voluntarily signed the informed consent form before any study related procedures
- Subjects must be males or females who are 18-85 years of age
- Subjects must have moderate to severe chronic, generalized periodontitis with pockets of 5 mm – 8 mm probing depth in at least 2 pockets per contralateral quadrants in one arch (study teeth)
- Subjects must be committed to the study and the required follow-up visits
- Subjects must be in good general health as assessed by the Investigator at time of surgery.

**Exclusion Criteria**

- Subjects taking or intending to take any medications during the duration of the study that will potentially affect healing and inflammation
- Subjects who are currently heavy smokers (defined >10 cigarettes per day or >1 cigar per day) or who use chewing tobacco
- Subjects being treated with systemic antibiotics or subjects that were treated with systemic antibiotics within 3 months prior to treatment in this study
- Subjects with uncontrolled diabetes
- Subjects that are immunocompromised or immunosuppressed
- Subjects that cannot provide informed consent
- Subjects with drug or alcohol abuse
- Subjects that have undergone periodontal root planing or periodontal surgery in the last 6 months
- Subjects that are pregnant
- Subjects with necrotizing periodontitis or periodontitis related to systemic disease
- Teeth with pockets with probing depth > 9 mm will not classify as study teeth
- Teeth with pockets or defects with furcation involvement will not classify as study teeth
- Teeth with mobility degree > 1 without splint will not classify as study teeth
- Subjects with test and control sites in the two quadrants on adjacent teeth
- Patients with compromised health conditions such as uncontrolled diabetes or uncontrolled systemic diseases, disorders or treatments that compromise wound healing, chronic high dose steroid therapy, bone metabolic diseases, radiation or immuno-oppressive therapy, and infections or vascular impairment at the surgical site
- Subjects with conditions or circumstances, in the opinion of the Investigator, which would prevent completion of study participation or interfere with analysis of study results

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All eligible patients will receive periodontal therapy consisting of minimally invasive surgery, plaque removal, and post-surgery oral hygiene instructions. Periodontal minimally invasive surgery is performed either alone (control quadrant) or in combination with Straumann® Emdogain® (test quadrant) for the treatment of periodontitis. Following periodontal surgery, control visits are scheduled at 2-3 weeks and at 1-, 3-, 6-, 9- and 12 months for clinical evaluations.

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Visit</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>Visit 1</td>
<td>Informed Consent / Screening &amp; Baseline</td>
<td>Within 14 Days of Enrollment</td>
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<tr>
<td>Visit 2</td>
<td>Minimally Invasive Scaling and Root Planing (SRP) and Emdogain® First Application</td>
<td>SURGERY - Point of Enrollment</td>
</tr>
<tr>
<td>Visit 3</td>
<td>Supragingival Plaque Removal and Emdogain® Second Application</td>
<td>2-3 Weeks after Surgery</td>
</tr>
<tr>
<td>Visit 4</td>
<td>Regular Periodontal Maintenance</td>
<td>1 Month after Surgery</td>
</tr>
<tr>
<td>Visit 5</td>
<td>Follow-up Visits</td>
<td>3 Months, 6 Months and 9 Months after Surgery</td>
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<tr>
<td>Visit 6</td>
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<td>Visit 7</td>
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<tr>
<td>Visit 8</td>
<td>Last Follow-up Visit / Study End</td>
<td>12 Months after Surgery</td>
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</table>

**Investigational Device**

Straumann® Emdogain® 0.15 ml, 0.3 ml, or 0.7 ml syringe (30 mg/ml)

**Registration Status**

Straumann® Emdogain® used in the study is CE-marked and has received FDA-clearance (PMA approval No. P930021 S013). The investigational device will be used within its cleared indications.
<table>
<thead>
<tr>
<th><strong>Primary Analysis</strong></th>
<th>The primary analysis will be conducted after all subjects complete the 12 months post-surgery visit.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>• Clinical Attachment Level (CAL) change</td>
</tr>
</tbody>
</table>
| **Secondary Endpoints** | • Change in Gingival Margin (GM)  
• Change in Probing Pocket Depth (PPD)  
• Change in Full Mouth Plaque Score (FMPS)  
• Change in Bleeding on Probing (BoP)  
• Change in root dentin hypersensitivity  
• Frequency of successful probing points (PPD < 5 mm)  
• Number of pockets that would normally be treated surgically that are converted to pockets that do not require surgical intervention. |
| **Interim Analysis** | Interim analysis will be done at 3 months post-surgery; optional interim analyses will be performed at 6 months and 9 months post-surgery. |
| **Interim Analysis Endpoints** | • Change in Clinical Attachment Level (CAL)  
• Change in Gingival Margin (GM)  
• Change in Probing Pocket Depth (PPD)  
• Change in Bleeding on Probing (BoP)  
• Change in root dentin hypersensitivity  
• Frequency of successful probing points (PPD < 5 mm)  
• Number of pockets that would normally be treated surgically that are converted to pockets that do not require surgical intervention.  
• Comparison of pain level between treatment groups at 1-2 days, 1 week, and 2 weeks after surgery. |
| **Statistical Consideration** | Statistics of the endpoints will be presented for raw values and change from baseline overall and by study center. The planned statistical testing to compare the treatment groups will be outlined in a Statistical Analysis Plan (SAP). |
| **Safety** | The patients will be monitored for adverse events by the Investigators until the end of follow-up for each patient. All device complaints and failures will be reported without delay to Straumann. |
| **Countries in which the Study will be performed** | United States and Canada |
| **Number of participating centers** | 4 centers |
| **Principal Investigators at Centers** | Dr. Veronique Benhamou, DDS  
Dr. Jennifer Hirsch Doobrow, DMD  
Dr. Pamela K. McClain, DDS  
Prof. Dr. Dr. h.c. Adrian Kasaj, M.Sc |
<p>| <strong>Number of Subjects Planned to be Enrolled</strong> | 50 subjects |</p>
<table>
<thead>
<tr>
<th><strong>Date of Study Initiation</strong></th>
<th>September 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Study Completion</strong></td>
<td>Enrollment through December 2016; Follow-up complete for all subjects by December 2017</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>Institut Straumann AG</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>This study and any amendments will be performed according to ISO 14155:2011, ICH E6(R1) Guideline on Good Clinical Practice (GCP) 1996, and conformed to the Declaration of Helsinki (last revised Fortaleza 2013). Local legal and regulatory requirements include compliance with 21 CFR 50, 21 CFR 54, and 21 CFR 56.</td>
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**Table 1 - Schedule of Assessments**

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<tr>
<th>Assessments</th>
<th>Visit 1*</th>
<th>Visit 2*</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
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<th>Visit 7</th>
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</table>

*Day 0 = Day 0 ± 2-3 days after Surgery*  
*1 Month ±1 Week after Surgery*  
*3 Months ±1 Week after Surgery*  
*6 Months ±2 Weeks after Surgery*  
*9 Months ±2 Weeks after Surgery*  
*12 Months ±2 Weeks after Surgery*  
*12-Month Follow-Up Visit / Study End*
<table>
<thead>
<tr>
<th>Assessments</th>
<th>Visit 1*</th>
<th>Visit 2*</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Informed Consent / Screening &amp; Baseline Visit</td>
<td>SURGERY (enrollment) Visit</td>
<td>Treatment Visit</td>
<td>1 Month Follow-Up Visit</td>
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*Visit 1 and Visit 2 can be conducted at the same office visit. If Visit 1 and Visit 2 are combined, a set of photographs should be taken pre and post-surgery.

**Pain scale will be sent home with the subject at Visit 2 and completed at 1-2 days, 1 week, and 2 weeks thereafter.
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1 Background and Rationale
The goal of regenerative periodontal therapy is the reconstruction of lost periodontal structures. Results from preclinical and clinical studies have shown that Emdogain® successfully promotes periodontal wound healing and regeneration, when used in conjunction with periodontal open flap surgery. Although Emdogain® has been proven successful to effectively promote periodontal regeneration as part of surgical procedures attempts to use the product for periodontal regeneration as part of minimally invasive surgery (i.e. flapless) procedures remain inconclusive and controversial or do not allow a definite conclusion on the effectiveness. Although the majority of reports does not support the use of Emdogain® in flapless periodontal procedures, few reports like the one of Wennström et al. indicate a potential effect of the product in flapless periodontal procedures. Specifically the authors have reported that Emdogain® provides an advantage in the early wound healing after flapless periodontal debridement.

A more thorough review of the available literature suggests that all attempts to establish the use of Emdogain® in flapless methods have lacked a systematic and standardized approach. In particular the preconditions as well as the details of the clinical workflow need to be carefully defined in order to analyze the success of regenerative procedures using Emdogain® in a flapless application. With this regards thorough debridement of the root/dentin surface but also removal of granulation tissue might be considered as a precondition for Emdogain® mediated regeneration of the periodontal tissues and periodontal attachment. As a consequence a defined and validated workflow is estimated to be necessary in order to achieve this goal. According to our knowledge such a systematic approach, which is considered to be necessary has not been applied yet to analyze the potential of Emdogain® in flapless periodontal procedures.

Mechanical debridement can be effectively achieved by manual (curettes) and power-driven tools (sonic and ultrasonic instruments) and can be partly combined with fiber optics in power-driven devices to improve the efficiency of root cleaning. In spite of the great efforts in the mechanical surface cleaning process it is well known today that pathogenic bacteria especially remain in the biofilm residues and also inside the tissue and cause reinfection and inflammation. More recent and advanced debridement strategies combine such approaches with laser-therapy, specifically in combination with photosensitizers (= antimicrobial photodynamic therapy, aPDT) to achieve full mechanical and microbiological debridement of the periodontal defect, which cannot be achieved by mechanical strategies alone.
To our knowledge as of today a validated and standardized workflow, which leads to a nearly complete mechanically and microbiologically cleaned root surface as starting point to evaluate the healing potential of Emdogain® in minimally invasive surgery application does not exist. Furthermore the selection criteria for clinical preconditions to allow treatment by the envisaged flapless workflow needs to be defined, such as inclusion criteria related to the type of periodontal defect, i.e. type, depth, width, and amount of granulation tissue, etc.

2 Study Objectives

A concept paper was developed by an independent expert group to identify and define the most important criteria within a clinical workflow using Emdogain® as part of the Scaling and Root Planing (SRP) minimally invasive surgical procedure for periodontal therapy and to standardize the workflow in order to optimize the regenerative potential of Emdogain®. In addition to defining the parameters within the workflow, the authors of the concept paper defined the preconditions and inclusion criteria, as well as exclusion criteria, to help select the appropriate patient population for treatment.

The concept paper is a basis for this study, which aims to provide a clinical assessment of the treatment workflow through a series of controlled cases. The controlled cases in this study will help to further define the workflow and evaluate the workflow based on clinical practicability and usability.

Furthermore this controlled case series will be used to obtain a first indication for the potential of Emdogain® in minimally invasive surgical procedures. Depending on the outcome of this pivotal study future steps in the project will include a defined clinical trial in a larger patient population. This clinical trial will be based on the knowledge gained from these initial controlled cases.

Future steps will also include the transfer of the standardized workflow into daily practice by assessing the conditions under which the workflow can be used and under which it cannot be recommended any more.

The aim of this controlled study is to assess the clinical outcomes and patient reported outcomes of using minimally invasive surgical procedure with Emdogain® as an adjunct (test treatment) or without Emdogain® (control treatment).

2.1 Primary Objective

To evaluate the regenerative potential of Emdogain® by looking at differences in Clinical Attachment Level (CAL) between the test and control treatments.
2.2 Secondary Objectives

To evaluate the regenerative potential of Emdogain® by looking at differences in:

- Gingival Margin (GM)
- Probing Pocket Depth (PPD)
- Full Mouth Plaque Score (FMPS)
- Bleeding on Probing (BoP)
- Post-surgical pain, and
- Root dentin hypersensitivity

between the test and control treatments.

3 Study Design

3.1 Type and Design of Study

This study is a post-market, prospective, split-mouth, controlled, multi-center study. Split-mouth design: each patient receives two treatments that are randomly assigned to either the right or left quadrant of the maxillary or mandibular arches.

- Test Treatment: Minimally Invasive Scaling and Root Planing (SRP) and applications of Emdogain®
- Control Treatment: Minimally Invasive Scaling and Root Planing (SRP) alone

3.2 Intended Use

Emdogain® is intended as an adjunct to periodontal surgery as a topical application onto exposed root surfaces to provide regeneration of tooth support lost due to periodontal disease or traumas. Emdogain® is indicated for the treatment of the following conditions:

- Intrabony defects due to moderate to severe periodontitis
- Mandibular degree II furcations with minimal interproximal bone loss
- Gingival recession defects in conjunction with surgical coverage procedures such as the coronally advanced flap technique
- Emdogain® is also indicated for use in a minimally invasive surgical technique in esthetic zones to optimize tissue height for intrabony defects only.

This study will be looking at the use of Emdogain® in minimally invasive surgical technique to optimize tissue height for intrabony defects.
PrefGel® is intended for topical application onto exposed root surfaces during periodontal surgery in order to remove the smear layer, prior to the application of Emdogain®.

3.3 Study Treatments

The workflow consists of:

Baseline evaluation:

The initial periodontal examination is conducted at the Visit 1 and includes a complete periodontal charting, including Pocket Probing Depth (PPD), Gingival Margin (GM), Bleeding on Probing (BoP), and Full Mouth Plaque Score (FMPS). This examination will be used to determine eligibility for the study based on inclusion/exclusion criteria (Section 3.7.1 and Section 3.7.2). Also, these are the baseline data used for the statistical analysis.

Treatment:

After qualification for the study, the subject will be randomized and treated with minimally invasive Scaling and Root Planing (SRP). An initial application of Emdogain® is performed during the SRP treatment for one quadrant (test). SRP alone will be performed in the contralateral quadrant (control). In addition, PrefGel® is applied on the test quadrant only (prior to the initial application of Emdogain®).

Based on the reported literature on how long Emdogain® remains in periodontal pockets\textsuperscript{11,10} a second application will be carried out 2-3 weeks after the initial Emdogain® application for the test quadrant to ensure longer presence of Emdogain® in the defect. Postoperative treatment is detailed in Section 5.2.3.

Re-evaluation and Follow-Up:

At 3 months, 6 months, 9 months, and 12 months after the initial application of Emdogain®, re-evaluations will be carried out in order to identify residual pockets that are indicated for perio-surgery (PPD ≥ 5 mm). This study design, including a dual application of Emdogain®, clearly aims to differentiate this treatment workflow from the approaches that have been reported in the literature.

3.4 Study Endpoints

The primary analysis will be conducted after all subjects complete the 12 months post-surgery visit:

3.4.1 Primary endpoint

- Change in Clinical Attachment Level (CAL)
3.4.2 Secondary endpoints

- Change in Gingival Margin (GM)
- Change in Probing Pocket Depth (PPD)
- Change in Full Mouth Plaque Score (FMPS)
- Change in Bleeding on Probing (BoP)
- Change in root dentin hypersensitivity
- Frequency of successful probing points (PPD < 5 mm)
- Number of pockets that would normally be treated surgically that are converted to pockets that do not require surgical intervention

Additional analysis will be done at 3, 6, 9 months post-surgery:

3.4.3 Additional endpoints

- Change in Clinical Attachment Level (CAL)
- Change in Gingival Margin (GM)
- Change in Probing Pocket Depth (PPD)
- Change in Bleeding on Probing (BoP)
- Change in root dentin hypersensitivity
- Frequency of successful probing points (PPD < 5 mm)
- Number of pockets that would normally be treated surgically that are converted to pockets that do not require surgical intervention
- Comparison of pain level between treatment groups at 1-2 days, 1 week, and 2 weeks after surgery.

3.5 Study Sample Size
The study will enroll 50 subjects at 4 centers.

3.6 Study Duration
The study is expected to enroll up to 50 subjects through December of 2016. The subject's participation in the study is expected to be 12 months and consists of 8 study visits.
3.7 Study Population

The study population will consist of male or female patients aged 18 to 85, with moderate to severe chronic, generalized periodontitis with pockets of 5 mm – 8 mm probing depth in at least 2 pockets per contralateral quadrants in one arch. Subjects will be recruited at the clinics where the Investigators are practicing in the United States and Canada and possibly through referring dentists’ offices. Subjects will also be recruited from a University dental clinic in Germany. Each subject will sign a written consent statement prior to any study procedures.

Subjects who provided consent in writing will be evaluated for eligibility during the screening visit and immediately prior to randomization. Patients will be screened based on the inclusion and exclusion criteria presented below.

3.7.1 Inclusion Criteria

All of the inclusion criteria must be met to qualify for this study:

- Subjects must have voluntarily signed the informed consent form before any study related procedures
- Subjects must be males or females who are 18-85 years of age
- Subjects must have moderate to severe chronic, generalized periodontitis with pockets of 5 mm - 8mm probing depth in at least 2 pockets per contralateral quadrants in one arch (study teeth)
- Subjects must be committed to the study and the required follow-up visits
- Subjects must be in good general health as assessed by the Investigator

3.7.2 Exclusion Criteria

If any of the following are met during screening, the subject or teeth must be excluded from the study and will not classify as subjects or study teeth.

- Subjects taking or intending to take any medications during the duration of the study that will potentially affect healing and inflammation
- Subjects who are currently heavy smokers (defined >10 cigarettes per day or >1 cigar per day) or who use chewing tobacco
- Subjects being treated with systemic antibiotics or subjects that were treated with systemic antibiotics within 3 months prior to treatment in this study
- Subjects with uncontrolled diabetes
- Subjects that are immunocompromised or immunosuppressed
- Subjects that cannot provide informed consent
- Subjects with drug or alcohol abuse
- Subjects that have undergone periodontal root planing or periodontal surgery in the last 6 months
- Subjects that are pregnant
- Subjects with necrotizing periodontitis or periodontitis related to systemic disease
- Teeth with pockets with probing depth ≥ 9 mm will not classify as study teeth
- Teeth with pockets or defects with furcation involvement will not classify as study teeth
- Teeth with mobility degree > 1 without splint will not classify as study teeth
- Subjects with test and control sites in the two quadrants on adjacent teeth
- Patients with compromised health conditions such as uncontrolled diabetes or uncontrolled systemic diseases, disorders or treatments that compromise wound healing, chronic high dose steroid therapy, bone metabolic diseases, radiation or immuno-suppressive therapy, and infections or vascular impairment at the surgical site
- Subjects with conditions or circumstances, in the opinion of the Investigator, which would prevent completion of study participation or interfere with analysis of study results

4 Study Products Description

4.1 General Product Information

Emdogain® is the investigational device in this study. PrefGel® is a product applied prior the application of Emdogain® but is not investigated in this study.

Straumann will provide the four centers with the necessary amount of Emdogain® and PrefGel® for the study. These products delivered for the study are to be used only for the subjects enrolled in the study and according to this protocol.

Emdogain® is a resorbable, implantable material for periodontal regeneration. It consists of hydrophobic enamel matrix proteins extracted from developing embryonal enamel of
porcine origin in a propylene glycol alginate carrier. Once applied onto an exposed root surface the protein self assembles into an insoluble three-dimensional matrix. Emdogain® is supplied in pre-filled, ready-to-use sterile, syringes and available in three sizes (0.15 ml, 0.3 ml, 0.7 ml of the gel). The 0.3 ml and 0.7 ml solution are delivered in packs of 1 syringe, while the 0.15 ml solution is delivered in packs of 5 syringes. The gel has a suitable viscosity to facilitate application directly onto root surfaces exposed during periodontal surgery.

The syringe containing 0.15 ml or 0.3 ml is intended for the treatment of one periodontal defect, while the one containing 0.7 ml for the treatment of up to 3 periodontally involved teeth.

PrefGel® 0.6 ml is a neutral Ethylenediaminetetraacetic acid, Edetic acid (EDTA) formulation intended for topical application onto exposed root surfaces during periodontal surgery in order to remove the smear-layer, prior the application of Emdogain®. Mechanical debridement of a root surface inevitably produces a smear-layer, which in turn may prevent or retard periodontal healing. PrefGel® is packaged in single-use sterilized pipettes.

Figure 1: Example of Emdogain® and PrefGel® syringes

4.2 Instructions For Use, Handling and Labeling
Emdogain® and PrefGel® will be used according to the Instructions For Use (Appendix 1 and Appendix 2) containing the approved indications, contraindications, warnings, precautions and sterilization instructions:

- IFU 700019 Emdogain® (US version)
- IFU 701910 Emdogain® (German version)
- IFU 700096 PrefGel®
Emdogain® is CE marked since 1995 (0.3 ml and 0.7 ml syringes) and 2012 (0.15 ml syringe), and received FDA marketing clearance since July 2012 (PMA approval No. P930021 S013). PrefGel® is CE marked since 1997 and subject of cleared 510(k) pre-market notifications K140878 since January 2007.

Emdogain® and PrefGel® will not be used if sterile package is opened or damaged prior to use. The package will be discarded or returned to manufacturer with the enclosed syringe and cannula if this is the case. Each pre-filled syringe is intended for use in one subject only and shall not be re-sterilized or reused. Reuse of single-use devices creates a potential risk of patient or user infection. Contamination of the device may lead to injury or serious illness of the patient.

The products will be removed from cold storage approximately 30 minutes before use applied at ambient temperature and within shelf life.

The plastic top of the syringe will be removed and the supplied application needle will be attached. Emdogain® will be used within 2 hours and any remaining gel will be discarded. The syringe and cannula are single use items.

The products must be used within their cleared indications.

All device deficiencies shall be reported by the Investigator to Straumann USA on the Device Deficiency Case Report Form as described under section 7.3.3.

4.3 Storage
The study products should be stored in their original container until used and its access shall be controlled.

Emdogain® and PrefGel® must be stored in a refrigerator (2 – 8 °C / 36°-46°F) upon arrival as indicated on the label of the packaging.

Separation of Emdogain® may occur, which is identified as a non-homogeneous gel. Homogenization of the separated material can be achieved by shaking down the gel from the top to the bottom of the syringe, turn around the syringe and repeat the procedure ten to fifteen times until homogenization returns.

4.4 Device Accountability
The Investigator must maintain an accurate and up-to-date accountability record of all study products, Emdogain® and PrefGel®, received, used, discarded (opened, but non-used) and returned during the course of the study. This information shall be recorded in the Device Accountability Record Log.
At each monitoring visit, the monitor will check the investigational device accountability for accuracy and completeness.

At the end of the study, the monitor or Straumann’s delegate conducting the closeout visit will perform a final reconciliation of the device accountability (cross check between the Device Record Accountability Log, the shipments delivery notes and the acknowledgement of device receipts).

4.5 Return of Study Device

After treatment of the last subject, any remaining unopened study products at site must be returned to Straumann and acknowledged for receipt. A copy of the acknowledgement of receipt must be filed in the Investigator Site File.

4.6 Risk Analysis, Risk/Benefits

The device risk analysis and risk assessment for Emdogain® and PrefGel® was conducted according to EN ISO 14971, part of the Straumann risk management process which ensures adequate handling of risk analysis, risk evaluation, risk control and evaluation of overall residual risk acceptability. Full results are included in the Risk Management Report for Emdogain®, PrefGel® and Osteogain Version 1.0 dated 1 September 2014. Refer to the Section 7.2.6 of this protocol for a description of the anticipated adverse device effects.

Read carefully the risks associated with the investigational device and the procedures involved in its use listed in Instructions For Use in Appendix 1 and Appendix 2 under Warning and Cautions/Precautions.

An anticipated benefit of the application of Emdogain® in combination with the minimally invasive surgical technique is the decrease of pain at treatment until 2 weeks after the surgery, as the decrease in root dentin hypersensitivity.

The identified hazards have been mitigated and the overall residual risks for the described medical devices are in the acceptable range.

In conclusion, the risks associated with the use of the Emdogain® and PrefGel® are acceptable when weighed against the benefits to the patient.
5 Study Procedures

5.1 Subject Screening and Baseline Evaluation

5.1.1 Informed Consent
The informed consent process will be conducted at Visit 1. It is the responsibility of the Principal Investigator, or a person designated by the Principal Investigator, to obtain informed consent from each subject participating in this study prior to any study related procedures. As part of the informed consent discussion with a potential subject, the Investigator or designee will provide an adequate explanation of the overall requirements/procedures of the study, purpose of the study, the nature of the planned treatment, any alternative procedures, and possible risks, complications, and benefits of the study. The Investigator or designee will also explain that the subjects are completely free to refuse to enter the study or to withdraw from the study at any time for any reason without prejudice.

The informed consent process will be approved by an Institutional Review Board (IRB) before consenting can begin. The Informed Consent Form (ICF) will be available in the primary language of the subject. This IRB approved consent form will be signed and dated by the subject and the person obtaining consent. Investigators will keep the original signed informed consent document in a secure location and a copy of the signed consent form will be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. All enrolled subjects will be informed of the new information, given a copy of the revised form and asked to provide consent to continue the study.

5.1.2 Inclusion and Exclusion Criteria
The inclusion and exclusion criteria will be evaluated at the screening visit. Subjects must fulfill all of the inclusion criteria and not meet any of the exclusion criteria. If this condition is not fulfilled, these patients will be considered as screen failures.

5.1.3 Medical and Dental History
Relevant medical history (e.g., allergic reactions, systemic diseases) and current medical conditions will be evaluated by the Investigator based on the information available. The information may be obtained from the subject's general physician or from oral communication with the subject.

Medical History:
Protocol Version 5.0, 29-Mar-2018
If patient needs pre-medication

- Smoker: "yes" or "no"; if "yes", how many
- If patient has been treated with systemic antibiotics, if "yes"; for how long
- If patient has uncontrolled diabetes: "yes" or "no"
- If patient is immunocompromised in anyway
- If patient has history of drug or alcohol abuse
- If patient is pregnant: "yes" or "no"

Dental History:

- If patient has undergone any periodontal root planing or periodontal surgery in the last 6 months

5.1.4 Demographics

Subject demographics, including age, gender, and race/ethnicity, will be documented at the screening visit.

For race, the subject may select American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White. For ethnicity, data will be collected on whether the subject is Hispanic or Latino.

5.1.5 Pregnancy Test

Women of child-bearing potential (women who are not surgically sterile or postmenopausal (defined as amenorrhea for >12 months)) must perform a pregnancy test (validated over-the-counter test) at Visit 1, before taking study required radiographs to confirm that the woman is not pregnant. The test result must be documented in the source data. A woman who is pregnant or planning to become pregnant at any point during the study duration cannot be enrolled in this study.

If a woman becomes pregnant during the study, a protocol deviation form should be completed. The woman should be followed for the duration of the pregnancy, without the study required radiographs, and the outcome of the pregnancy should be documented.
5.1.6 Concomitant Medication
Concomitant medication, procedures, and supportive therapies will be recorded at the screening visit. Any changes in the concomitant medications, procedures, and supportive therapies must be documented at each study visit until the end of the study.

5.1.7 Adverse Event Check
At each visit the Investigator should determine if any adverse events occurred since the last study visit by speaking with the subject and reviewing any dental and medical records. These Adverse Events (AEs), along with any adverse events from the current study visit, should be documented and reported as described in Section 7. of the protocol. In addition the Investigator should evaluate the status of any ongoing adverse events throughout the study as specified in Section 7.4.

5.2 Treatment Procedures
The treatment workflow is graphically presented in Appendix 3 and starts from Visit 2 – Surgery Visit.

5.2.1 Selection and Assignment of Quadrants
The inclusion and exclusion criteria will be reviewed (Section 3.7.1 and 3.7.2). If the subject remains eligible, randomized treatment assignment of a quadrant (test or control), will be done via randomization envelopes. At Visit 2, the Investigator or designee will open a sealed randomization envelope. The randomization envelope will identify the treatment assignment for the right and left quadrants, both in the same arch of the eligible patient. **Randomization envelopes must be open in sequential order.**

5.2.2 Surgery - Minimally Invasive Scaling and Root Planing and Emdogain®
First Application
Patients that have been randomized and have scaling and root planing with Emdogain® treatment during Visit 2 are considered enrolled in the study. Each subject will receive local anesthetic and be treated in one visit with a sequence of steps defined by the treatment assignment:

- **Test treatment:** For the quadrant assigned to scaling and root planing + Emdogain®, the following steps should be conducted for treatment: scaling and root planing, control of bleeding, application of PrefGel® (until there is clear overflow from the pocket) to remove any residual smear layer for 2 minutes, irrigation with sterile saline thoroughly, and application of Emdogain® starting apically and advancing coronally until there is clear overflow from the pocket.
• **Control treatment:** For the contralateral quadrant, assigned to scaling and root planing alone, the following steps should be conducted at the same visit as the test treatment: scaling and root planing and control of bleeding.

Mechanical debridement will be carried out in the manner commonly performed by the clinician (e.g., hand instrumentation, ultrasonic scalers with diamond tips). No antimicrobial agents or techniques (antibiotics or antisepsics, photodynamic therapy) will be applied during treatment. No vasoconstrictors (other than 1:100,000 or 1:200,000 epi in local anesthetic) or hemostatic agents will be used in surrounding soft tissues or pockets. Bleeding will be stopped by conventional techniques as much as possible. No sutures or periodontal dressings will be applied.

In order to standardize treatment across centers, only loupes or a microscope can be used as an assistive visual aid for debridement and removal of calculus from defects. Other quadrants not being evaluated in the study should be treated according to standard practice.

### 5.2.3 Plaque Removal and Emdogain® Second Application

After the surgery, all subjects will be given a periodontal cleaning with supragingival plaque removal for both the test and control quadrants at Visit 3. At this visit, Emdogain® will be re-applied to the test quadrant. In detail, this procedure involves no anesthesia, supragingival plaque removal at low power setting, no Prefgel® application, and application of Emdogain® will start apically and advance coronally (as appropriate for treatment assignment group).

Other quadrants not being evaluated in the study should be treated according to standard practice.

### 5.2.4 Post Treatment Instructions

After both procedures described above, at Visit 2 and 3, the subject will be sent home with post-treatment instructions that includes the use of antiseptic oral rinse (e.g., 0.12% chlorhexidine solution) for one week with no brushing during that time. The subject will also be instructed to refrain from flossing or using a waterpik for one month after the treatment. No local or systemic antibiotics should be prescribed. When brushing, soft brushes are recommended to be used on a 90° angle on the tooth surfaces in order to avoid sulcular brushing.
5.2.5 Supragingival Prophylaxis
Supragingival Prophylaxis includes plaque control and supra-gingival teeth cleaning, with no subgingival instrumentation.

5.2.6 Regular Periodontal Maintenance
At each follow-up visit, regular periodontal maintenance will be provided and may include plaque control, supra-gingival teeth cleaning, or any other necessary therapy that is standard practice at the study center.

5.3 Outcome Assessments
The following measurements will be taken by the same examiner throughout the study.

5.3.1 Pocket Probing Depth (PPD)
Probing Pocket Depth (PPD) will be measured by recording the distance from the gingival margin to the bottom of the probable pocket at 6 sites (mesiofacial, facial, distofacial, distolingual, lingual, mesiolingual) on the teeth in the contralateral quadrants.

Assessment will be done at screening/baseline visit and from the 3-month to the last follow-up visit.

5.3.2 Gingival Margin (GM)
The Gingival Margin (GM) measurements will be performed simultaneously with the PPD measurements. GM will be measured by recording the distance from the Cemento-Enamel Junction (CEJ) to the margin of the gingiva at 6 sites (mesiofacial, facial, distofacial, distolingual, lingual, mesiolingual) on the teeth in the contralateral quadrants.

In periodontal sites with a visible CEJ (see Figure 2), the distance from the CEJ to the margin of the gingiva will be measured as noted in the diagram below.

In periodontal sites with no visible CEJ (see Figure 3), the periodontal probe will be inserted into the periodontal pocket and angulated approximately 45° in order to manually detect the reference line. The depth of insertion into the periodontal pocket will be recorded as the GM.

A negative value for the GM indicates gingival recession. A positive value for the GM indicates the gingiva is covering the CEJ. A zero indicates the gingiva is at the same level as the CEJ.
Assessment will be done at screening/baseline visit and from the 3-month to the last follow-up visit.

Figure 2: Measurement of the GM when the CEJ is visible.

Figure 3: Measurement of the GM when the CEJ is not visible.
5.3.3 Clinical Attachment Level (CAL)
Clinical Attachment Level (CAL) measurements will be derived from the PPD and GM measurements as follows:

\[ \text{CAL} = \text{PPD} - \text{GM} \]

Measurement will be calculated from the PPD and GM values taken at screening/baseline visit and from the 3-month to the last follow-up visit.

5.3.4 Bleeding on Probing (BoP)
Bleeding on probing (BoP) will be measured on the teeth in the contralateral quadrants. The presence of bleeding will be documented as a "yes" or "no" response on 6 sites (mesiofacial, facial, distofacial, distolingual, lingual, mesiolingual).

Assessment will be done at screening/baseline visit and from the 3-month to the last follow-up visit.

5.3.5 Full Mouth Plaque Score (FMPS)
The Full Mouth Plaque Score (FMPS) according to O'Leary et al should be documented as an indicator for the oral hygiene on each single tooth of the mouth mesial, distal, facial, and lingual. Disclosing agents should not be used to assess plaque.

The FMPS will be assessed with the following formula:

\[ \frac{\text{# of tooth surfaces with plaque}}{\text{total number of tooth surfaces}} \times 100 = \text{FMPS} \]

Assessment will be done at Visit 1, Visit 3 and at the 12-month follow-up visit.

5.3.6 Pain Scale
Postsurgical pain will be measured on a Visual Analog Scale (VAS) (Appendix 4) by asking the patient to assess their pain at three time points after treatment with minimally invasive SRP and Emdogain® application. The three time points will be 1-2 days, 1 week, and 2 weeks after surgery.

Subjects will be given a paper Case Report Form (CRF) to bring home with them and mark their responses on the VAS. The subject will mark a 100 mm scale with a vertical line directly on the CRF. The subject will then return the form to the clinic and a
measurement will be made from the left of the scale to the point of the first marking from the subject to determine the value in mm.

5.3.7 Root Dentin Hypersensitivity
Presence of root dentin hypersensitivity is examined by isolating the neighboring teeth and using a conventional air blast for three seconds on the study tooth. The root dentin hypersensitivity is recorded as "none" (no reaction from the subject), "mild" (sensible with no pain), "moderate" (sensible with slight pain), or "severe" (sensible with pain that persists for a while). Assessment will be done at Visit 2 – Minimally Invasive Scaling and Root Planing and Emdogain® First Application (SURGERY) and from the 3-month to the last follow-up visit.

5.3.8 Radiographs
Peri-apical radiographs, panoramic radiograph, or Cone Beam Computed Tomography (CBCT) of the teeth in the contralateral quadrants will be taken according to the standard practices at the clinic. Ideally images should be taken at screening/baseline visit and at the 12-month visit.

5.3.9 Intra-oral Photographs
Intra-oral photographs will be taken at each study visit to document the initial appearance of the soft tissue and the subsequent healing of the soft tissue after the study treatment. The camera alignment should be perpendicular to the labial surface of the tooth being photographed. Photographs should document all of the treated teeth. A minimum of 5 mm of the marginal soft tissue should be present in the photograph.

Three photographs are required at each visit, including one standard full mouth, and two of the right and left teeth in occlusion. If Visit 1 and Visit 2 are combined, a set of photographs should be taken pre and post-surgery.

Photographs will be labeled for easy identification of the subject and study visit.

5.4 Protocol Related Procedures

5.4.1 Point of Enrollment
The point of enrollment in this study is defined as the moment when the subject is randomized and the investigational device Emdogain® is applied at the study site, during the surgery taking place at Visit 2.

Patients enrolled in the study will be documented in the Patient and Enrollment Log.
5.4.2 Withdrawal Criteria and Procedures
Any subject may withdraw from the study at any time without prejudice and will be offered an alternative treatment for his/her dental condition. Subjects will be advised of the need for the prescribed follow-up visits for their ongoing care, well-being, and collection of any safety data.

- The Investigator may withdraw any subject from the study in the case of:
- Non-compliance with the protocol
- Failure to attend the follow-up visits
- Serious adverse event or adverse event, in the opinion of the Investigator, which prevents the subject’s further participation in the study.

The subject withdrawal will be documented on a study termination form and must include the reason for the subject withdrawal. All efforts will be made to capture the primary study endpoint for each subject prior to withdrawal.

If the subject signed consent, but did not meet the inclusion/exclusion criteria, then the subject will be considered a screen failure. This will be documented on the study termination form.

If at any time a subject requires surgery during the course of the study in the region of the mouth being evaluated in the study, then the subject should be withdrawn from the study.

5.4.3 End of Study
Once the subject is seen for the final visit at 12 months post-surgery, the subject will have completed the study. This will be documented on a study completion form.

5.4.4 Subject Replacement Procedures
Subjects that are considered screen failures will be replaced.

Subjects that have been randomized, have scaling and root planing with Emdogain® treatment during Visit 2 are considered enrolled and will not be replaced.

5.4.5 Protocol Deviations
Deviations from the procedures established in the protocol are not permitted. If a deviation occurs, the deviation will be recorded on the Protocol Deviation Log. The sponsor shall be notified immediately of any deviations in informed consent and
inclusion/exclusion criteria (i.e. major deviations), and the IRB shall be notified according to the requirements of the local IRB.

Any deviation from the protocol (including deviations from the expected study visit windows, i.e. minor deviations) may jeopardize the study outcome. Non-compliance of the subjects, as well as of the Investigators, may lead to the closure of the respective study center.

6 Schedule of Assessments

An overview of the schedule of assessments is provided in the Table 1 - “Schedule of Assessments”.

6.1 Visit Windows

Subjects need to be seen within the following windows:

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Visit Name</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>Informec Consent/Screening &amp; Baseline Visit</td>
<td>14 - 0 Days before enrollment</td>
</tr>
<tr>
<td>Visit 2</td>
<td>Final Screening Randomization Minimally Invasive Scaling and Root Planing and Emdogain® First Application</td>
<td>RANDOMIZATION AND SURGERY - Point of enrollment Day 0</td>
</tr>
<tr>
<td>Visit 3</td>
<td>Supragingival Plaque Removal and Emdogain® Second Application</td>
<td>2-3 Weeks ± 2-3 Days</td>
</tr>
<tr>
<td>Visit 4</td>
<td>Regular Periodontal Maintenance</td>
<td>1 Month ± 1 Week</td>
</tr>
<tr>
<td>Visit 5</td>
<td>3-Month Follow-up Visit</td>
<td>3 Months ± 1 Week</td>
</tr>
<tr>
<td>Visit 6</td>
<td>6-Month Follow-up Visit</td>
<td>6 Months ± 2 Weeks</td>
</tr>
<tr>
<td>Visit 7</td>
<td>9-Month Follow-up Visit</td>
<td>9 Months ± 2 Weeks</td>
</tr>
<tr>
<td>Visit 8</td>
<td>12-Month Follow-up Visit</td>
<td>12 Months ± 2 Weeks</td>
</tr>
</tbody>
</table>

6.2 Visit 1 – Screening & Baseline Visit

This visit should be completed within 14 days prior to the Surgery Visit (Visit 2). An initial evaluation will be conducted to determine whether the subject meets the study inclusion and exclusion criteria.

The following procedures and assessments will be performed and recorded at the screening visit:

- Informec consent
- Medical & Dental history
• Demographics
• Pregnancy Test
• Inclusion/exclusion criteria
• Initial Periodontal Examination and Assessment of Periodontal Status
• Collection of baseline clinical measurements:
  o Pocket Probing Depth
  o Gingival Margin
  o Bleeding on Probing
  o Full Mouth Plaque Score
• Radiographs
• Photographs
• Concomitant Medications
• Adverse Events check

6.3 Visit 2 – Minimally Invasive Scaling and Root Planing and Emdogain\textsuperscript{®} First Application (SURGERY)

Visit 2 needs to be completed within 14 days from the Screening & Baseline Visit. It is possible to conduct Visit 1 and Visit 2 at the same office visit.

The following will be conducted during this visit:

• Final review of inclusion/exclusion criteria and determination of subject eligibility.
• Identification of the contralateral quadrants and treatment assignment
• Root Dentine Hypersensitivity at the study teeth
• Randomization (if subject meets all eligibility criteria).
• Minimally invasive scaling and root planing, control of bleeding, application of PrefGei\textsuperscript{®} irrigation with sterile saline, and first application of Emdogain\textsuperscript{®} for teeth treated in test quadrant.
• Scaling and root planing and control of bleeding for teeth treated in control quadrant.
• Pain scale completion by the patient
• Post treatment oral hygiene instructions

• Photographs

• Concomitant Medications

• Adverse Events check

6.4 Visit 3 - Supragingival Plaque Removal and Emdogain® Second Application

The patient will be recalled for a visit at 2-3 weeks after the surgery, for a periodontal cleaning with supragingival plaque removal and reapplication of Emdogain® according to the treatment assignment.

In particular, the subject will have the following procedures and/or evaluations performed and documented:

• Supragingival plaque removal for both test and control quadrants

• Emdogain® re-application to teeth treated in test quadrant (no PrefGel® re-application)

• Full Mouth Plaque Score

• Pain scale completion by the patient

• Post treatment oral hygiene instructions

• Photographs

• Concomitant Medications

• Adverse Events check

6.5 Visit 4 – Periodontal Maintenance

The subject will be recalled for a visit at 1 month after Surgery.

In particular, the subject will have the following procedures and/or evaluations performed and documented:

• Supragingival Prophylaxis.

• Photographs

• Concomitant Medications

• Adverse Events check
6.6 Visit 5 – Follow-up Visit 3 Months

Subjects will be recalled at 3 months after Surgery.

The subject will have the following procedures and/or evaluations performed and documented:

- Data Collection including: Pocket Probing Depth, Gingival Margin, Bleeding on Probing, Root Dentin Hypersensitivity at the study teeth
- Regular Periodontal Maintenance
- Photographs
- Concomitant Medications
- Adverse Events check

6.7 Visit 6 – Follow-up Visit 6 Months

Subjects will be recalled at 6 months after Surgery.

The subject will have the following procedures and/or evaluations performed and documented:

- Data Collection including: Pocket Probing Depth, Gingival Margin, Bleeding on Probing, Root Dentin Hypersensitivity at the study teeth
- Regular Periodontal Maintenance
- Photographs
- Concomitant Medications
- Adverse Events check

6.8 Visit 7 – Follow-up Visit 9 Months

Subjects will be recalled at 9 months after Surgery.

The subject will have the following procedures and/or evaluations performed and documented:

- Data Collection including: Pocket Probing Depth, Gingival Margin, Bleeding on Probing, Root Dentin Hypersensitivity at the study teeth
- Regular Periodontal Maintenance
- Photographs

Protocol Version 5.0, 29-Mar-2018
• Concomitant Medications
• Adverse Events check

6.9 Visit 8 – Follow-up Visit 12 Months / Study End

Subjects will be recalled at 12 months after Surgery.

The subject will have the following procedures and/or evaluations performed and documented:

• Data Collection including: Pocket Probing Depth, Gingival Margin, Bleeding on Probing, Root Dentin Hypersensitivity at the study teeth, with addition of Full Mouth Plaque Score (FMPS)
• Regular Periodontal Maintenance
• Radiographs
• Photographs
• Concomitant Medications
• Adverse Events check

7 Evaluation of Adverse Events

For the avoidance of doubt, all AE/SAEs as defined below should be collected for all subjects from the time of screening (Visit 1).

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or the comparator, or events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.2 Serious Adverse Event (SAE)

Any adverse event that:
• led to a death
• led to a serious deterioration in the health of the subject, that either resulted in
o a life-threatening illness or injury, or
o a permanent impairment of a body structure or a body function, or
o in-patient or prolonged hospitalization, or
o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

- led to fetal distress, fetal death, or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered to be a serious adverse event.

7.1.3 Device Deficiency (DD)
A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.

7.1.4 Adverse Device Effect (ADE)
An ADE is an adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Any adverse event which the clinical investigator believes has even a possible relationship to the device, the event will be classified as and ADE.

7.1.5 Serious Adverse Device Effect (SADE)
An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.6 Unanticipated Serious Adverse Device Effect (USADE)
An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

7.1.7 Anticipated Serious Adverse Device Effect (ASADE)
An ASADE is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Summary of the classification for adverse events:

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Non-device related</th>
<th>Device or procedure related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-serious</td>
<td>Adverse Event (AE)</td>
<td>Adverse Device Effect (ADE)</td>
</tr>
<tr>
<td>Serious</td>
<td>Serious Adverse Event (SAE)</td>
<td>Serious Adverse Device Effect (SADE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticipated Unanticipated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticipated Serious Adverse Device Effect (ASADE) Unanticipated Serious Adverse Device Effect (USADE)</td>
</tr>
</tbody>
</table>

7.2 Assessment of Adverse Events

In the event of an adverse event, the Investigator or another suitably qualified clinician who is trained in recording and reporting AEs and have been delegated to this role (such delegation must be captured in the study site delegation log) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event.

Each adverse event should be assessed for seriousness, relationship to the study device or the procedure, severity and expectedness, as described below, by the Investigator.

7.2.1 Seriousness

An adverse event will be described as serious if it meets the definition in Section 7.1.2. The rationale for the assessment shall be provided in a short narrative.

7.2.2 Relationship to the Study Device

The Investigator should assess the relationship of the adverse event to the study product and study procedure. The relationship should be assessed using the following categories:

- Definitely Related – There is a reasonable causal and temporal relationship between the treatment with the study device and the adverse event.
- Possibly Related – The relationship between the treatment with the study device and the adverse event is less likely; however, the determination that there is no relationship cannot be made.
- Not related – No relationship between treatment with the study device and the adverse event is obvious.
NOTE: Device deficiencies that might have led to an SAE are always related to the medical device.

The Investigator shall provide rationale for the assessment of the expectedness in a short narrative on the AE/ADE Report Form.

7.2.3 Relationship to the Procedure

The Investigator should assess the relationship of the adverse event to the surgical procedure (i.e. application or reapplication of Emdogain®). The relationship should be assessed using the categories described in Section 7.2.2.

The Investigator shall provide rationale for the assessment of the expectedness in a short narrative on the AE/ADE Report Form.

7.2.4 Severity

Each adverse event should be assessed for its severity, or the intensity of an event experienced by a subject, using the following:

- **Mild** – events are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** – events that introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- **Severe** – events interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment

The maximum severity observed is to be recorded, except if there is a significant worsening in an AE/ADE severity after device intake, then the change will be tracked as a new AE/ADE record as follows:

- The same wording describing the original AE/ADE must be used.
- Outcome of the initial entry should be designated as 'worsened'.
- The end date of the previous AE/ADE must equal the start date of the new AE/ADE.

7.2.5 Outcome

The outcome should reflect the status of the adverse event at the moment of recording.
- **Resolved without sequelae** - The subject fully recovered from the event without any sequelae. This option also applies when it is unknown whether there are sequelae.

- **Resolved with sequelae** - The subject's condition stabilized despite the persistence of sequelae (e.g., lesion or medical condition which is a consequence of the event). This option does not apply to irreversible congenital anomalies (see under “ongoing”).

- **Ongoing** - The subject has not yet recovered from the event. By convention, in the case of an irreversible congenital anomaly, the “Ongoing” option should be chosen and understood as “Not recovered/Not resolved”. The same applies to conditions that are not yet resolved, but are controlled by medication (e.g., diabetes, epilepsy) and therefore may not have any symptoms.

- **Worsened** - The severity of the AE/ADE increased.

- **Fatal** - The event is related to a death; whether it caused death or contributed to it. If the subject died of a different cause, prior to resolution of the AE/ADE, the outcome of this AE/ADE should designated “Ongoing”, and not “Fatal”, and an end date should not be specified.

- **Unknown**: Knowledge of the current status of the AE/ADE is truly not available to the Investigator (i.e. event was ongoing at last observation, but no further contact with the subject could be established). However, all efforts should be made to determine the outcome of any AE, especially that of an SAE/SADE.

### 7.2.6 Expectedness

If the adverse event is judged to be related to the device, the investigator will make an assessment of expectedness based on knowledge of the reaction and any relevant product information as documented in the IFU and current protocol. The event will be classed as either:

- **Expected**: the reaction is consistent with the effects of the device listed in the IFU and protocol;

- **Unexpected**: the reaction is not consistent with the effects listed in the IFU and protocol.

The Investigator shall provide rationale for the assessment of the expectedness in a short narrative on the AE/ADE Report Form.
Potential expected adverse events following the application of Emdogain® by type and in order of severity, observed in the clinical trials, are listed below:

<table>
<thead>
<tr>
<th>Adverse Event type</th>
<th>Adverse Event description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitization</td>
<td>Low rate of sensitization to Emdogain® as a result of repeated use.</td>
</tr>
<tr>
<td>Local soft tissue reactions</td>
<td>Local redness, inflammation, soreness, gingival irritation, hematoma/ecchymosis, oral candidiasis, tissue necrosis/cratering, angulitis, herpes-like blisters, hypoesthesia (burning and itching reaction on the tongue), oral mucosal reaction, fibrin layer, discoloration.</td>
</tr>
<tr>
<td>Local tooth-related reactions</td>
<td>Increased tooth mobility, hypersensitive root surfaces (root sensitivity), pain.</td>
</tr>
<tr>
<td>General reactions</td>
<td>Urticaria, itching skin reaction, gastrointestinal disturbances, urogenital disturbances.</td>
</tr>
</tbody>
</table>

Potential expected adverse device effects following the application of PrefGe®: Reversible and short duration procedure-related dentin hypersensitivity may occasionally occur.

7.3 Procedure for Reporting Adverse Events

Adverse event reporting will begin at the time a subject provides written informed consent and ends after a subject withdraws from the study or completes the final study visit.

For screen failure subjects, any AEs, ADEs, and DDs that occur from the time of informed consent up until the date on which the subject is deemed ineligible for the study will be recorded on a case report form.

Only one AE/ADE Report Form or SAE/SADE Report Form should be completed per event.

To ensure patient confidentiality, the following reports will include the patient number only.

7.3.1 AE Reporting

In the occurrence of an adverse event (AE), the AE/ADE Report Form should be completed in a timely manner. Safety reporting to the Institutional Review Board (IRB) should occur according to the requirements of the local IRB.
7.3.2 SAE Reporting

In the occurrence of a serious adverse event (SAE), expedited reporting requirements are followed. The SAE/SADE Report Form should be completed within 24 hours of awareness of the event and sent to Straumann by fax or email.

Safety reporting to the Institutional Review Board (IRB) should occur according to the requirements of the local IRB.

It is recognized that in many cases SAEs will be treated in a medical rather than a dental environment and the Investigator may not have immediate knowledge of the event. The Investigator should report an SAE as soon as he/she has knowledge of the event within the above time frame irrespective of when the actual event occurred.

7.3.3 DD Reporting

The Investigator should report all Device Deficiencies (DD) by completing the Device Deficiency Case Report Form.

When a device deficiency leads to a potential AE (e.g. bleeding, pain, swelling, infection, peri-implantitis), the AE/ADE Report Form needs to be additionally completed in a timely manner.

Moreover, device deficiencies with SADE potential (e.g. nerve encroachment, sinus perforation, etc.) must be recorded in the SAE/SADE Report Form and follow the expedited reporting requirements (within 24 hours).

7.3.4 ADE Reporting

Adverse device effects (ADE) must be recorded and submitted to Straumann by completing the AE/ADE Report Form in a timely manner. Safety reporting to the Institutional Review Board (IRB) should occur according to the requirements of the local IRB.

7.3.5 SADE Reporting

In the occurrence of a serious adverse device effect (SADE), expedited reporting requirements are followed. The SAE/SADE Report Form should be completed within 24 hours of awareness of the event and sent to Straumann by fax or email.
7.3.6 Additional Safety Reporting

Straumann will report additional safety information to the centers that is relevant to the protocol or study device and may affect the risk/benefit ratio, the rights, safety or welfare of subjects, or the integrity of the study. Such reports may include notification of any changes to the Instructions for Use, any publications or interim reports, or any product recalls.

7.4 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of this study must be monitored and followed-up by the Investigator until one or more of the following have occurred:

- The AE is resolved,
- Pathological laboratory findings have returned to normal,
- Steady state has been achieved, or
- It has been shown to be unrelated to the study products

It is the responsibility of the sponsor to cooperate with the Investigator to assure that any necessary additional therapeutic measures and follow-up procedures are performed.

8 Statistical Analysis Procedures

The statistical analysis principles described below will be supplemented by a detailed Statistical Analysis Plan (SAP).

8.1 Sample Size Calculation

This is a pilot study with a goal to create a standardized treatment workflow that can later be tested in further studies to show that Emdogain® can effectively promote periodontal regeneration as part of the minimally invasive surgical procedure. This study will help to define the selection criteria for clinical preconditions to allow treatment via the envisaged surgical treatment workflow. A sample size of 50 subjects will be adequate for this pilot phase considering a possible dropout rate of up to 15%.

8.2 General Statistical Methods

A qualified statistician using validated statistical software will perform all statistical analysis according to the planned statistical testing provided in the Statistical Analysis Plan (SAP).
95% confidence intervals will be calculated based on the SAP to support the descriptive statistics, where necessary.

Unless otherwise specified, the data will be summarized for non-missing subjects in tables listing the number of subjects, and the mean, 25% percentile, median, 75% percentile minimum, maximum, standard deviation in each treatment group for continuous data (e.g., PPD, GM, CAL, FMPS and pain), or number of subjects and percentage in each treatment group for categorical data (e.g., Bleeding on Probing, Root Dentin Hypersensitivity), as appropriate. In general the denominator for the percentage calculation will be based upon the total number of subjects (N) in the study population, unless otherwise specified.

8.2.1 Baseline Characteristics
The baseline data are presented on the basis of all screened subjects. They are collected at the Visit 1 and include: Medical & Dental History, Demographics, Inclusion & Exclusion Criteria, Concomitant Medications, Adverse Event Check, PPD, GM, CAL, FMPS, and Pain (see details in Section 5.1 and 5.3).

To assess balance in baseline characteristics, the distribution of each baseline variable of interest will be compared between the two treatment groups, i.e. test and control quadrants of the same arch. Continuous variables will be summarized using mean, median, standard deviation, 95% confidence interval, and range; testing between the two groups will be based on a two-sample t-test (or Wilcoxon rank-sum test as appropriate). Categorical variables will be summarized using counts and percentages, and differences between treatment groups will be assessed using a Chi-square test (or Fisher's exact test as appropriate).

8.2.2 Treatment Procedures
The treatment procedures data is presented on the basis of all enrolled patients. They are performed at Visit 2 and 3 (see details in Section 5.2).

Summaries of treatment procedures and supportive measures will be presented by assigned treatment group (test and control). Detailed information regarding the treatment procedures will be presented in listings (i.e. details per patient).

8.2.3 Other Data Summaries
Protocol deviations will be summarized by deviation type and study center.

Concomitant medications will be presented in listings and also summarized by drug category.
Adverse events will be presented in listings and also summarized by event category.

8.2.4 Subject Disposition
A description of subject disposition falling in various subgroups of interest, such as consented, screen failures, enrolled, withdrawn early, completed study, will be provided by study center. Moreover, a detailed description providing the reason of any screen failures or early withdrawal by subgroup will be done.

8.2.5 Missing Data
Every effort will be made to minimize the amount of missing data. If subjects drop out of the study prior to completing their primary endpoint assessment, every effort will be made to measure their primary endpoint immediately prior to discontinuation if possible.

Techniques for handling missing data and the presence of outliers will be provided in the Statistical Analysis Plan.

8.3 Planned Statistical Analysis
Two analyses will be performed: A primary analysis at 12 months and an interim analysis at 3 months post-surgery. An optional interim analysis at 6 and 9 months post-surgery may also be performed. Descriptive summary statistics will be computed for all endpoints of the primary and interim analysis.

The data of the four study centers will be pooled. Pooling is justified by applying a high degree of standardization of study procedures and investigator training.

8.3.1 Primary Analysis of Primary Endpoint
Change in Clinical Attachment Level (CAL) between the surgery and 12 months post-surgery will be measured as the primary endpoint.

Statistics of the primary endpoint will present the seven-point scales (mean, standard deviation, minimum, 25% percentile, median, 75% percentile and maximum) of the change in CAL on the site of interest for each treatment group.

8.3.2 Primary Analysis of Secondary Endpoints
Statistics of the secondary endpoints will present the seven-point scales of the change in GM and PPD on the site of interest for each treatment group, and the change in
FMPS. Additionally, the percentage of Bleeding on Probing and Root Dentin Hypersensitivity on the site of interest will be presented by treatment group.

Investigator’s assessment on the number of pockets that would normally be treated surgically that are converted to pockets that do not require surgical intervention will be presented.

The influence of pocket size as a factor impacting outcomes will also be evaluated with pocket size being categorized into two groups: 5 - 6 mm pockets and 6 – 8 mm pockets. Other covariates may be considered in the exploratory analysis.

8.3.3 Interim Analysis of Endpoints

Interim analysis will be performed for all above endpoints between the surgery and 3 months post-surgery. Optional interim analyses will be performed at 6 months and 9 months post-surgery, as applicable.

In addition, the seven-point scales (mean, standard deviation, minimum, 25% percentile, median, 75% percentile and maximum) of the change in pain for each treatment group will be presented at 1-2 days, 1 week and 2 weeks after surgery.

9 Data Management

The general data management procedures are described below, details can be found in the separate Data Management Plan (DMP).

Required clinical data for this study will be collected and recorded in the clinical database using a paper Case Report Form (CRF) for all study subjects from whom informed consent is obtained. Site numbers and subject numbers will be used to track subject information throughout the registry. The Principal Investigator or authorized designee is responsible for the timely completion and signature of all CRFs.

All original CRFs will be retrieved from the site by the study monitor and sent to the data management. Double data entry and computer programmed error checks will be carried out by data management personnel for inconsistent, illogical and/or missing data. If validation of data leads to discrepancies, data management will generate queries. The timely resolution of the queries is under the responsibility of the monitor and the Investigators at site. The query process is an ongoing process starting with the first data entered into the database.

The electronic clinical database used for this study has a security system that prevents unauthorized access to the data and any deletion of data (audit and edit trail). All above mentioned tasks will be carried out according to Straumann Standard Operating Procedures, Protocol Version 5.0, 29-Mar-2018
except for those tasks performed by Straumann contracted Contract Research Organizations (CRO), where the CRC procedures shall be used.

10 Obligations of the Principal Investigator

10.1 Investigator Compliance
The Investigators must work according to standard ethical practice as laid down by their professional body and insert the product according to what is described in the handling procedures and the IFU for the products investigated in this clinical study. In addition, they must work in accordance with the “Declaration of Helsinki” (last revision Fortaleza 2013, Appendix 5), the ISO 14155:2011, GCP, and with local legal and regulatory requirements.

The Investigators will ensure that the study is conducted in compliance with this protocol and the Clinical Study Agreement. Furthermore, they are responsible of conducting the informed consent process (section 5.5.1).

11 Study Management

11.1 Regulatory and Ethical Requirements

11.1.1 Informed Consent
Written informed consent will be obtained from all subjects prior to study participation as described in Section 5.1.1.

11.1.2 Institutional Review Board
Prior to initiation of any study procedures, the protocol and informed consent will be submitted to each local Institutional Review Board (IRB) for review and approval. In addition, any amendments to the protocol or informed consent will be reviewed and approved (if necessary) by the IRB. The study will not begin until the required approval from the IRB has been obtained. Any additional requirements imposed by the IRB shall be followed.

The Investigator will provide the appropriate reports to the IRB during the course of the clinical study including the following:

- Informing the IRB of the study progress periodically as required, but at a minimum annually
- Reporting any unanticipated serious adverse device effects within 10 working days of becoming aware of the event
- Reporting any deviations from the protocol that adversely affect the risk/benefit ratio, the rights, safety, or welfare of the participants, or integrity of the study
- Providing any other reports requested by the IRB

11.1.3 Study registration
This protocol will be registered at clinicaltrials.gov at the study start.

11.2 Record Management
The following will be required from the investigator prior to the initiation of the study:
- A signed confidentiality agreement
- Signed and dated curriculum vitae of the Investigator(s) and a copy of his/her dental license
- Signed Financial Disclosure
- A signed copy of the final protocol and any amendments
- A signed copy of the clinical study agreement with the sponsor
- IRE approval letter and IRB approved informed consent document

11.2.1 Case Report Forms
Required clinical data for this study will be collected using a paper CRF for all study patients from whom informed consent is obtained. Site numbers and patient numbers will be used to track patient information throughout the study to respect confidentiality.

The Principal Investigator or authorized designee will be responsible for the accuracy of the data entered on the CRFs from source documents, query resolution and signature of all CRFs. The Investigator will also allow a Straumann representative and/or regulatory bodies to review the data reported on the CRFs with the source documents as far as is permitted by local regulations.

11.2.2 Source Documents
Source documents are defined as the original point of entry of a specific data point. Source documents will include, but are not limited to, progress notes, electronic data computer printouts, radiographs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons.
11.2.3 Records/Data Retention

Original radiographs, photographs, and study documents will be maintained at the study center in a file established for this study. All study documentation needs to be stored at the study center for at least twenty (20) years following the completion of the study, as specified by the sponsor. The Investigator should have access to the study documents in order to answer any queries associated with the study. All other study records will be kept by Straumann once the study has been completed. These records will be maintained at Straumann according to Straumann’s Standard Operating Procedures (SOP).

11.3 Monitoring

Straumann will assign a qualified individual to monitor the study.

The study specific monitoring procedures for performing site visits, frequency, data verification, data corrections, adverse event reporting and tracking, device accountability, regulatory documents review, visit communication and reporting are described in the separate Monitoring Plan.

11.3.1 Pre-Study Meetings

After selection of all Investigators, Pre-Study Meetings were conducted during the preparation phase for the study, at congresses, to explain the study requirements and ensure the sites are fully capable and equipped to participate in the study.

11.3.2 Study Initiation Visit

Once a site receives IRB approval and before enrollment in the study starts, the monitor will schedule a site initiation visit in order to make sure all study documents are in place and that all the site personnel that will participate in the study are trained on the study procedures. The monitor will ensure during the study initiation that the Investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study:

- Understands the clinical protocol and relevant items outlined in the protocol (including inclusion/exclusion criteria, AE and SAE reporting requirements)
- Understands and accepts the obligations to obtain informed consent
- Understands how to document study data (especially the importance of having supporting documentation for AE assessment)
• Understands the information outlined in the Investigator’s brochure, including proper device usage

• Understands aspects of study device accountability (i.e. how to obtain the device, how to store the device, how to document device receipt, usage and return)

• Understands and accepts the obligation to obtain IRB review and approval of the protocol and informed consent, and to ensure continuing review of the study by the IRB

• Has adequate facilities and access to an adequate number of suitable subjects to conduct the study

11.3.3 Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically during the course of the study to supervise study procedures as defined in the Monitoring Plan, but at a minimum annually to review the following:

• The study is in compliance with the currently approved protocol/amendment(s); deviations will be discussed with the responsible Investigator; documented, and reported to the sponsor and IRB (according to the IRB policy).

• The study is in compliance with Good Clinical Practice (GCP) and with the applicable regulatory requirements

• Only authorized Investigators/clinical personnel are participating in the clinical investigation

• Device accountability including adequate supply at center, proper storage, and documentation of device traceability.

• The reported study data entered on CRFs are accurate, complete, and verifiable from source documents

• All adverse events and serious adverse events are reported correctly. In cases where there is missing information about an adverse event or missing evidence to support the Investigator’s assessment, a monitor will review and discuss the adverse event with the responsible Investigator.

• The reason for a subject’s withdrawal has been documented
The investigator is providing to the sponsor the necessary study records for a thorough review of the study’s progress.

11.3.4 Study Closeout Visit

After the last subject has completed the study, all the data have been collected (there are no more outstanding AEs/SAEs & all outstanding Queries/data clarification forms have been resolved appropriately), the database is locked and ready for statistical analysis, the closeout visit will be conducted at the center. The following tasks should be completed at the last visit by Straumann or the monitor:

- Ensure that device accountability is complete
- Ensure that the documentation and clinical investigation requirements were met
- Collect outstanding documents (original signed tracking logs) and ensure that the Site Files are complete
- Ensure that adverse events were reported to the IRB according to the IRB’s policy and that the IRB was notified in writing of the study completion
- Review any outstanding questions from the Clinical Investigation Report and organize the signature process
- Organize the archiving of all study-related documents and remind the investigator of the obligation to retain the records and to notify Straumann in case the site is informed of an inspection by a regulatory authority.

11.4 Study Termination or Premature Termination

At study termination, a Clinical Investigation Report will be prepared by the sponsor, even if the study was terminated prematurely. The report will contain a summary of the study results and made available to the participating investigators.

The study can be terminated earlier at the discretion of the investigator or the sponsor in the case of any of the following:

- Occurrence of adverse device effects unknown at the start of the study with respect to their nature, severity, and duration, or the unexpected excessive incidence of known adverse device effects
- New scientific knowledge obtained after the start of the study showing the ethical claim of the study is no longer valid
Patients will be advised of the need for follow-up visits for their ongoing care and well-being.

11.4.1 Study Discontinuation

The study Center will be closed and the study terminated under the following circumstances:

- The Center is not recruiting a sufficient number of subjects or is unlikely to recruit a sufficient number of subjects
- The Center does not respond to study management requests
- Repeated protocol violations have been discovered that affect the integrity of the study or the study data.

11.5 Protocol Amendments

Once the first subject has entered the study, any part of this study plan can be amended upon agreement of the sponsor and the participating Principal Investigators throughout the clinical investigation. Protocol changes will be kept to a minimum. Only those changes that are deemed essential to the successful completion of the protocol will be considered.

The reasons and justifications for the amendment will be included with each amended section of the document, and the amendment will include a version number and date. Once the Investigator and the sponsor have accepted the changes, a written amendment to the protocol will be sent to the Investigator for signature.

All significant protocol changes affecting the scientific soundness of the study or the rights, safety, or welfare of subjects which occur after the initial IRB approval, must be submitted for approval by each center to the IRB as an amendment to the original protocol before the changes can be implemented by the Investigator. Each investigational center will send a copy of the IRB approval letter for the amendment to Straumann.

Requests for clarification statements to the protocol shall be discussed with the study monitor. The clarification statements will be sent to each Investigator and will be kept in the appropriate file.

11.6 Publications

Analysis of data will be conducted by Straumann and the final report will be prepared by Straumann with input from the Investigators. Any publications or presentations utilizing the
data from this study must be reviewed by Straumann prior to submission according to the time frame specified in the Clinical Study Agreement.
12 Protocol Signature Page

Protocol: CR 01/15

Study Title: Straumann® Emdogain® Application In Conjunction With Minimally Invasive Surgical Technique For Periodontal Disease Treatment: A Split-Mouth Design Study.

Version: Version 5.0; Date: 29-Mar-2018

I have read the foregoing protocol and agree to conduct the study as outlined. I agree that the examinations and follow-up visits required by the study protocol are in accordance with the standard treatment plan for dental implant subjects.

Signature:

______________________________  ________________________________
Clinical Center Name             Clinical Center Number

______________________________  ________________________________
Printed Name of Investigator     Signature of Investigator

______________________________
Date

Received by Sponsor:

______________________________  ________________________________
Printed Name of Study Manager    Signature of Study Manager

______________________________
Date
13 References


Appendix 1 – Instructions For Use IFU 700019 (US version) - Emdogain®

Emdogain® is a resorbable, implantable material for periodontal regeneration. It consists of hydrophobic enamel matrix proteins extracted from developing embryonal enamel of porcine origin in a propylene glycol alginate carrier. Once applied onto an exposed root surface the protein self-assembles into an insoluble three-dimensional matrix. Emdogain is supplied in a pre-filled, ready-to-use sterile, syringe. The gel has a suitable viscosity to facilitate application directly onto root surfaces exposed during periodontal surgery.

Indications for Use
Emdogain is intended as an adjunct to periodontal surgery as a topical application onto exposed root surfaces. Emdogain is indicated for the treatment of the following conditions:

- Intrabony defects due to moderate or severe periodontitis
- Mandibular degree II furcations with minimal interproximal bone loss
- Gingival recession defects in conjunction with surgical coverage procedures such as the coronally advanced flap technique
- Emdogain is also indicated for use in a minimally invasive surgical technique in esthetic zones to optimize tissue height for intrabony defects only.

In cases of wide defects or where soft tissue support is desired, Straumann® Emdogain can be used in conjunction with a bone graft material. For further information on the use of Emdogain with bone graft materials, please refer to “For Straumann® Emdogain in Conjunction with Bone Graft Material in Wide Defects” in the Clinical Procedure Section of these Instructions.

Contraindications
Emdogain should not be used in patients with disorders or conditions including, but not limited to the following: uncontrolled diabetes or other uncontrolled systemic diseases, disorders or treatments that compromise wound healing, chronic high dose steroid therapy, bone metabolic diseases, radiation or other immuno-suppressive therapy and infections or vascular impairment at the surgical site.
Warnings
- Immunological studies suggest that a small number of patients may become sensitized to Endogain as a result of repeated use. Please use caution in patients predisposed to allergic reactions and follow patients receiving repeated use closely. Post-market experience has indicated that the sensitization adverse reaction rate is low. Required treatment has ranged from no intervention needed to analgesics and/or antihistamines.
- The safety and effectiveness of Endogain has not been established in patients undergoing anticoagulant therapy. Careful consideration should be given before using Endogain for these patients.
- Endogain is intended for application around teeth only. Gain of tooth support occurs only to the level on the root surface covered by the repositioned oral soft tissue. Therefore, Endogain should be used in areas where there is adequate tissue for root coverage. Endogain should be used only after plaque and calculus have been removed from the diseased site.

Precautions
- Appropriate oral hygiene is necessary for proper healing to take place. Please refer to the "Clinical Considerations" section for additional information.
- Clinical and radiographic evaluation should be performed before treatment.
- It is important to maintain asepsis during surgery.

Clinical Considerations
Periodontal devices should only be used by those practitioners familiar with current periodontal therapy and periodontal surgical procedures. Improper technique may yield suboptimal results. Preclinical and radiographic surgical evaluation is imperative. Special effort to maintain asepsis during surgery is most important. To prevent postoperative infection and to optimize healing, the use of an antiseptic mouth rinse is recommended for a period of 3 to 6 weeks post-surgery. Antibiotics may be used if deemed appropriate based on the nature of the severity of the disease/defect and the clinician's judgment.

Since maintenance of a stable wound is a critical factor for success, the patient should be instructed not to brush in the area where surgery has been performed until 6 weeks postoperatively. However, consistent with conventional post-surgical care, the patient should be subjected to “professional tooth-cleaning” as needed. Recommendations for appropriate oral hygiene measures, including methods for interproximal cleaning, should be based on the clinician's judgment, due to the need for extended wound stability, and the awareness that regain of clinical attachment and alveolar bone has been shown to continue for more than a year following treatment with Endogain. In addition, clinicians have reported on enhanced wound healing in cases treated with Endogain while patients report less post-surgical discomfort following the use of Endogain.

Clinical studies with Endogain demonstrated clinical attachment gain and alveolar bone gain in intrabony defects associated with moderate to severe periodontitis and in mandibular degree II furcations with an interproximal bone level at or above the fons of the furcation. Radiographic evidence of new bone gain provided the primary support for the use of Endogain in intrabony defects, while horizontal furcation depth as assessed during re-entry was the primary outcome parameter when evaluating the use of Endogain in mandibular degree II furcation involvements. Adjunctive use of Endogain in the treatment of recession type defects has demonstrated equal or better root coverage compared to conventional treatments, as well as an increase in the amount of keratinized tissue.

Histological studies have demonstrated periodontal regeneration (newly formed cementum, periodontal ligament, and alveolar bone). Clinical data demonstrates the long-term stability of regenerated tissue. As in any periodontal surgical therapy, defect morphology, surgical technique and host response are important parameters for successful outcomes.

The following table presents results from three clinical trials evaluating the use of Endogain in intrabony defects. The data is reported as the difference between the clinical measurements taken at baseline before the initial operation and the clinical measurements taken at the designated follow-up periods. For the clinical parameters of pocket depth reduction and clinical attachment gain, the data are also expressed as the percent difference between the results of the surgical procedure alone and treatment with Endogain. Radiographic bone gain is reported as the linear measurement and as the percentage of the initial bone loss that was regained.
Adverse Reactions/Complications
A distinction of adverse events seen due to the use of Emdogain alone could not be performed because Emdogain is labeled for use in conjunction with conventional periodontal surgery for which there are associated risks. The adverse events by type and in order of severity, observed in the clinical trials, are listed below.

Local Soft Tissue Reactions
Local redness, inflammation soreness, gingival irritation, hematoma/ecchymosis, oral candidiasis, tissue necrosis/cratering, angulitis, herpes-like blisters, hypoesthesia (burning and itching reaction on the tongue), oral mucosal reaction, fibrin layer, discoloration.

Local Tooth-related Reactions
Increased tooth mobility, hypersensitive root surfaces (root sensitivity), pain.

General Reactions
Urticaria, itching skin reaction, gastrointestinal disturbances, urogenital disturbances

The following additional adverse events and surgical complications, although not observed in the studies, may be related to this type of surgical procedure and have the potential to occur: postoperative hemorrhage, infection, would dehiscence, sloughing of tissue, paresthesia, bleeding, loosening of sutures.

Directions for Use
Do not use if sterile package is opened or damaged prior to use. To prevent possible contamination, discard or return damaged package with the enclosed syringe and cannula.

Each pre-filled syringe is intended for use in one patient only.

The syringe containing 0.15 ml and 0.3 ml are intended for the treatment of one periodontal defect. The syringe containing 0.7 ml is intended for the treatment of up to three periodontally involved teeth.

1. Take out the Emdogain from cold storage approx. 30 minutes before use and allow it to assume ambient temperature.

2. Remove the plastic tip of the syringe.

3. Carefully attach the supplied application needle.

4. Use Emdogain within 2 hours and discard any remaining gel.

Syringe and cannula are single use items. Do not re-sterilize or re-use syringe or application needle. Be aware that bending the needle may cause breakage.
Storage
The product should be stored in a refrigerator (36°-46°F) upon arrival.

Separation of Straumann Emdogain may occur. Separation of Straumann Emdogain is identified as a non-homogeneous gel. Homogenization of the separated material can be achieved by shaking down the gel from the top to the bottom of the syringe, turn around the syringe and repeat the procedure ten to fifteen times until homogenization returns.

Clinical Procedure
For Straumann® Emdogain in Conjunction with Periodontal Flap Surgery

1. Anesthetize the area selected for surgery by block and/or infiltration anesthesia. Avoid injection of local anesthetic with a vasoconstrictor into the interdental papilla or marginal gingiva.

2. Make intra-crevicular incisions. Then, if judged appropriate, make one or two vertical releasing incisions extending out into the alveolar mucosa. Raise full-thickness (mucoperiosteal) flaps on the buccal and palatal/lingual surfaces of the tooth. Preserve as much of the gingival connective tissue in the flap as possible. Maintain viability of periodontal cells by hydration of the soft tissue with saline.

3. Only remove the granulation tissue adherent to the alveolar bone and any associated osseous defects necessary to provide full access and visibility to the root surfaces.

4. Remove subgingival plaque and calculus.

5. Remove remaining smear layer by cleansing the root surface with Straumann® PrefGel (EDTA) for 2 minutes. Rinse thoroughly with sterile saline. Avoid contamination of the cleaned root surfaces with saliva or blood after the final rinse.

6. Immediately apply Emdogain onto the exposed root surfaces, starting at the most apical bone level. Apply Emdogain to fully cover the exposed root surface areas. Overflow of surplus material during suturing should occur.

7. Complete coverage of the interproximal area and optimal soft tissue adaptation are essential. If deemed appropriate, a periosteal tenostomy at the base of the flap may be used to facilitate coronal repositioning of the soft tissue. Suture materials appropriate for extended stable closure are preferred.

8. The patient should be advised to rinse daily with an antiseptic mouth rinse (e.g., 0.1–0.2% chlorhexidine solution) until 3–6 weeks post-surgery. Antibiotics may also be used if deemed appropriate based on the clinician’s judgment.

9. Sutures may be removed when clinical healing of flaps and the root/soft tissue interface are stable or when they no longer add to the stability of the healing wound.
10. The patient should be instructed not to brush in the area where surgery has been performed until 6 weeks postoperatively. However, “professional tooth-cleaning” should be performed as needed. After the initial healing period, patients are instructed in appropriate tooth cleaning measures, including methods for interproximal cleaning. Recommendations for oral hygiene should be based on the need to maintain extended wound stability.

Clinical Procedure
For Straumann® Emdogain in Conjunction with a Minimally Invasive Surgical Technique

1. Anesthetize the area selected for surgery by block and/or infiltration anesthesia. Avoid injection of local anesthetic with a vasoconstrictor into the interdental papilla or marginal gingival.

2. Remove subgingival plaque and calculus from the root surface. Following mechanical debridement, the epithelial lining of the pocket is removed. Apply pressure to the site with a gauze sponge for 1 minute to stop bleeding. Thoroughly rinse the area with sterile saline to remove any blood and or saliva.

3. Remove remaining smear layer by cleansing the root surface with Straumann® PrefGel™ (EDTA) for 2 minutes. Rinse thoroughly with sterile saline. Avoid contamination of the conditioned root surface with saliva or blood after the final rinse.

4. Immediately apply Emdogain onto the root surface, starting at the bottom of the periodontal defect. Apply Emdogain to fully cover the root surface until an overflow of material occurs.

5. Optimal soft tissue adaptation is essential. Sutures can be used to closely adapt the soft tissues to the tooth surfaces.

6. The patient should be advised to rinse daily with an antiseptic mouth rinse (e.g. 0.1–0.2 % chlorhexidine solution) until 3–6 weeks post-surgery. Antibiotics may also be used if deemed appropriate based on the clinician’s judgment.

7. Sutures may be removed when clinical healing and the root/soft tissue are stable.

8. The patient should be instructed not to brush in the area where surgery has been performed until 6 weeks postoperatively. However, “professional tooth-cleaning” should be performed as needed. After the initial healing period, patients are instructed in appropriate tooth cleaning measures, including methods for interproximal cleaning. Recommendations for oral hygiene should be based on the need to maintain extended wound stability.

Clinical Procedure
For Straumann® Emdogain in Conjunction with Coronally Advanced Flap for Treatment of Recession Type Defects

1. Anesthetize the area selected for surgery by infiltration and, if needed block anesthesia. Avoid injection of local anesthetic with a vasoconstrictor into the interdental papilla or marginal gingival.

2. Scale and plan the exposed root surface to remove plaque, calculus, root surface irregularities and, if judged appropriate, to reduce prominence.

3. Make a sulcular incision at the site of the recession. Extend the incision horizontally into the adjacent interdental area slightly coronal to the level of the soft tissue margin of the recession.

4. Make two vertical divergent releasing incisions at the mesial and distal line angle connected to the horizontal incision.
5. Raise a full-thickness [mucoperiosteal] flap until the mucogingival junction is passed.

6. Make a cut through the periosteum and continue to raise a split-thickness flap by means of a blunt dissection. The aim is to eliminate any muscle tension on the flap margins and allow for a passive and tension-free coronal positioning of the flap at the level of the CEJ.

7. De-epithelialize the buccal aspect of the interdental papilla to create a connective tissue bed for suturing the coronally advanced flap.

8. Remove remaining smear layer by cleansing the root surface with Straumann® PreGel (EDTA) for 2 minutes. Rinse thoroughly with sterile saline. Avoid contamination of the conditioned root surface with saliva or blood after the final rinse.

9. Immediately apply Emdogain to fully cover the exposed and conditioned root surface.

10. Coronally position the flap and secure it at the level of the CEJ by suturing the flap into the recipient bed, i.e. the de-epithelialized papilla. Also close the vertical incisions with lateral sutures. Use suture materials for extended stable closure. No pressure should be applied to the flap after suturing.

11. The patient should be advised to rinse daily with an antiseptic mouth rinse (e.g. 0.1–0.2 % chlorhexidine solution) until 4 weeks post-surgery. Patients should also be instructed to avoid muscle traction or other trauma to the treated area for the same period.

12. Sutures may be removed when clinical healing of the flap is stable or when they no longer add to the stability of the healing wound.

13. The patient should be instructed not to brush in the area where surgery has been performed until 4 weeks postoperatively. However, "professional tooth-cleaning" should be performed as needed. After the initial healing period, patients are instructed in a tooth cleaning technique, which minimizes apically directed trauma on the gingival margin/soft tissues of the treated tooth.

**Clinical Procedure**

For Straumann® Emdogain in Conjunction with Bone Graft Material in Wide Defects

The use of bone graft materials in wide defects may be necessary in order to prevent tissue prolapse and interference in the bone-healing process. The performance of Emdogain with various bone grafting substitutes had not been evaluated in the original marketing application. Straumann conducted a review of the published dental literature to learn of the safety and effectiveness of combining Emdogain with various bone substitutes. A meta-analysis of the published literature (see references listed below) concluded that Emdogain, whether combined with autograft, allograft, bone derived xenograft, β-tricalcium phosphate, or Bioactive Glass, or implanted by itself, produced an improvement in average CAL gain, average PD reduction, and average recession gain over baseline values. These results demonstrated that the combination of Emdogain and any one of the bone graft materials studied did not adversely affect wound healing outcomes. Therefore, in cases of wide defects or where soft tissue support is desired, Straumann® Emdogain can be used in conjunction with a bone graft material.

It is important to note that due to the nature of the Meta analysis process and variation in study protocols evaluated, Meta analyses can introduce confounding variables affecting conclusions drawn from them. This Meta analysis of the use of Emdogain with bone grafting materials does not constitute a complete or rigorous evaluation of the use of Emdogain in conjunction with bone graft materials.

In the case where a bone grafting substitute is desired, it is recommended to prepare and condition the root surface as described elsewhere within these instructions, followed by application of Straumann® Emdogain onto the root surface, avoiding an overflow of the material. The remaining Straumann Emdogain may be used to moisten the bone substitute material.
Alternatively, the bone substitute material may be moistened using a medium described in the instructions from the bone substitute manufacturer. The moistened bone substitute is then applied to fill the defect to the highest level of bone loss before closing the flap.

Reference List


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<th>Clinical Attachment Gain (mm, SD)</th>
<th>% of Total Gain Attained</th>
<th>Pocket Depth Reduction (mm, SD)</th>
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<td>2.2 (0.4, 1.0)</td>
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<td>0.0 (0.3, 0.4)</td>
</tr>
</tbody>
</table>

*The table represents data for the patient group in the control group.*

**p < 0.05, p < 0.01, p < 0.001, respectively.**

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Please note
Practitioners must have appropriate knowledge and instruction in the handling of the Straumann product described herein ("Straumann Product") for using the Straumann Product safely and properly in accordance with these instructions for use.

The Straumann Product must be used in accordance with the instructions for use provided by the manufacturer. It is the practitioner’s responsibility to use the device in accordance with these instructions for use and to determine, if the device fits to the individual patient situation.

Straumann Products with the CE mark fulfill the requirements of the Medical Devices Directive 93/42/EEC.

Valid for
Upon publication of these instructions for use, all previous versions are superseded.

© Institut Straumann AG, 2010. All rights reserved. Straumann® and/or other trademarks and logos from Straumann® mentioned herein are the trademarks or registered trademarks of Straumann Holding AG and/or its affiliates.

Do not re-use
Rx only
U.S. Federal law restricts this device to sale by or on the order of a licensed dentist

STERILE A
Sterilized using aseptic processing techniques

REF
Catalogue number

Use by date

Manufacturer

Caution, consult accompanying documents
<table>
<thead>
<tr>
<th>Language</th>
<th>Instructions for use: Straumann® Emdogain®</th>
</tr>
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<tbody>
<tr>
<td>English</td>
<td>2-4</td>
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<tr>
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</table>
English Instructions for use: Straumann® Endogain®

CAUTION: U.S. federal law restricts this device to sale by or on the order of a dental professional.

1. Product Description
Straumann® Endogain® is a retrievable, implantable material and supports periodontal regeneration, which takes place over more than 1 year. It consists of hyaluronic acid and hence proteins extracted from developing bovine umbilical cord of pareion origin in a proprietary gelatinous matrix. The gel has a suitable viscosity to facilitate application directly onto root surfaces exposed during periodontal surgery. Once applied onto the exposed root surface, the protein constituent is solubilized into an insoluble three-dimensional matrix and creates a suitable environment for selective periodontal cell migration and attachment, which establishes both bone supporting tissues. Subsequent information of new attachment, alveolar bone can also regenerate due to the osteogenic capacity of the restored periodontal ligament (Endogain®) is degraded by enzymatic processes of normal wound healing.

Straumann® Endogain® is supplied in pre-filled syringes and available in three sizes: 0.25 ml, 0.5 ml, and 0.7 ml of the gel. The different syringes allow adapting the amount to the size and number of defects in one single patient as part of one surgical session. Each syringe is intended for single use on one patient only.

The following procedure steps are offered for customer convenience:
- Straumann® Endogain® Multifitpack combination: 1 x syringe with Endogain® (endos) 0.25 ml or 0.5 ml filling volume and 1 x syringe of Straumann® FreeCel®.

2. Intended use
Endogain® is intended for topical application in conjunction with periodontal surgery to provide regenerative tooth support lost to periodontal disease or trauma.

Straumann® Endogain® may be used to support the soft tissue wound-healing processes as part of oral surgical procedures.

3. Indications
- Endogain® has been shown to be effective in sites with periodontal defects more than 1 mm deep and associated with root surface features that are thought to have some role in attachment biology such as bone loss, furcation involvement, gingivitis, or severe gingival recession.
- Endogain® has also been shown to be effective in sites with periodontal defects that are less than 1 mm deep and associated with root surface features that are thought to have some role in attachment biology such as bone loss, furcation involvement, gingivitis, or severe gingival recession.

4. Contraindications
Based on the results of the clinical studies, the following patient population are contra-indicated: patients with severe systemic conditions including, but not limited to the following: uncontrolled diabetes, or other uncontrolled systemic diseases, disorders of treatments that compromise wound healing, chronic high-dose steroid therapy, bone metabolic diseases, radiation or other immune-suppressive therapies, infection or other immune responses, or vascular insufficiency at the surgical site.

5. Side effects, interactions and precautions: complications with Straumann® products
In rare cases, clinical studies have reported the occurrence of general, procedure-related adverse events including but not limited to gingival bleeding, erosion, infections, infection, post-surgical pain and swellings, and abcess-like lesions.

6. Warnings
Immunological studies suggest that a small number of patients may become sensitized to Endogain® as a result of repeated use. Hence, caution in patients predisposed to allergic reactions and follow patients receiving repeated use. Post-market experience indicates that the sensitization adverse reaction rate is low. Repeated treatment has ranged from 12 to 12 months to 12 to 12 months in untreated conditions and to 12 to 12 months in treated conditions. The safety and effectiveness of Endogain® have not been established in patients undergoing anticoagulants and/or antiplatelet therapies. Careful consideration should be given before using Endogain® for these patients. Endogain® is intended for application around teeth only. Gain of tooth support occurs only at the level of the root surface covered by the repositioned alveolar soft tissue. Therefore, Endogain® should be used only in areas where there is appropriate tissue for root coverage. Endogain® should be used only after plaque and calculus have been removed from the diseased site.

7. Caution/Precautions
- Do not use sterile package if opened or damaged. To prevent possible cross contamination, discard or return damaged package and the enclosed device.
- Syringe and application device are single-use items. Do not reutilize or reuse syringe or application device. Once pre-filled syringes are intended for use in one patient only. Route of single-use devices creates a potential risk of patient or user infections. Contamination of the device may lead to injury or serious illness of the patient.
- The product should be stored at 2-8°C upon arrival.
- Site-specific anatomy, surgical management, wound stabilization, and post-surgical oral hygiene are critical factors for success.
- Be aware that bending the cannula when it is attached to the syringe may cause leakage of the syringe.

8. Note
Separation of Straumann® Endogain® may occur upon storage. Straumann® Endogain® is intended as a non-homogenous gel. Homogenization of the separated material can be achieved by shaking down the gel from the top to the bottom of the syringe, turning around the syringe, and repeat the procedure ten to fifteen times until homogenization is complete.

9. Procedure
1. Take out Endogain® from the storage, store at 2-8°C before use and allow to assume ambient temperature.
2. Carefully attach the supplied application cannula.
3. Use the Endogain® within 2 hours and discard any remaining gel.

In conjunction with conventional periodontal surgery:
1. Anesthetize the area selected for surgery by block and/or infiltration anesthesia. Avoid injection with a vasoconstrictor in the interdental papilla or marginal gingiva.
2. Make intraoral incisions, then, if judged appropriate, make one or two vertical incisions, extending only into the alveolar mucosa. Place full-thickness mucoperiosteal flaps.
3. Expose the bone defect and any associated defects necessary to prevent full access to the root surface.

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gival plaque and calculus. Remove remaining
smear layer by a clean surface cleaning with 
Straumann® Predent® EDTA for 2min or 5s
with citric or phosphoric acid, thoroughly
with water. Avoid contamination of the 
surgical area with saliva or dirt after the final
wash

4. Immediately apply Emogran® onto the ex-
posed root surfaces starting at the most apical
corner and apply Emogran® to fully cover
the exposed root surfaces. (Overflow of
starch material during wetting should occur)

5. Complete coverage of the interproximal area 
and optimal soft tissue adaptation is im-
portant if deemed appropriate. Periostal
elevation at the base of the flap may be 
used to facilitate coronal positioning of the
soft tissue. Starch materials appropriate for
extended stable coverage should be preferred.
Wound stability is critical to the outcome of
a regeneration procedure using Emogran®.
If the leakage between the root surface and
the healing connective tissues is broken, the
periodontal defect will readily epithelialize
resulting in a clinical failure.

6. The patients should be advised not to brush
daily with an antiseptic mouth rinse (p. 9-1 2)
chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

7. The patient should be instructed not to brush
the area where surgery has been performed
until 3 weeks postoperatively. Then only gentle
brushing with soft, loaded with a
"soft-bristle" method is recommended. No
scaler or interproximal tooth cleaning must
be performed until 6 weeks postoperatively.

8. Saliva may be removed when the flap and
the root surface tissue are stable, usually
within 6-3 weeks. Continued conventional
post-surgical care is however recommended.
No additional solutions are recommended.
Continuous healing of the interproximal area
and similar bone has been shown to continue
for more than a year, and should be treated
with care in this process.

In conjunction with coronally advanced
flap for treatment of recession type

Defects:

1. Anteriorize the area selected for surgery by
anesthesia, and control of bleeding.

Avoid injection of local anesthesia with a
volume sufficient to minimize the incidence of
marginal gingiva.

2. Plan and scale the exposed root surface to
remove plaque, calculus, and root surface
irregularities and, if judged appropriate, to reduce
premature

3. Make a subgingival incision at the site of the re-
cession. Extend the incision coronally into
the adjacent interproximal area slightly mann
the CEJ

4. Make two vertical incisions, releasing incisions
at the mesial and distal line angles connected
to the horizontal incision.

5. Raise a full-thickness (euphorically) flap
from the mucogingival junction to the
horizontal incision. The aim is to eliminate
any muscle tension on the flap margins
and allow for a passive and firm free coronal
positioning of the flap at the level of the CEJ.

De-epithelialize the buccal aspect of the gingival
margins to allow for a connective tissue
bed for suturing (euphorically) advanced flap

6. Condition the exposed root surface with
Straumann® Predent® EDTA for 2min or 5s
with citric or phosphoric acid, thoroughly
with water. Avoid contamination of the
conditioned test tissue with saliva or blood
after the final wash.

7. Immediately apply Emogran® to fully cover
the exposed and conditioned test surface.

8. Corroborate the flap and secure it at the
level of the CEJ by suturing the flap to the
recipient bed, i.e., the de-epithelialized papilla.

9. Place the sutures on the incision with the
flap margins, the submucosal materials for
stable coverage, and no pressure should be applied
to the flap after suturing.

10. The patient should be advised not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

11. The patient should be instructed not to brush
the area where surgery has been performed
until 3 weeks postoperatively. Then only gentle
brushing with soft, loaded with a
"soft-bristle" method is recommended. No
scaler or interproximal tooth cleaning must
be performed until 6 weeks postoperatively.

12. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

13. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

14. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

15. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

16. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

17. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

18. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

19. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.

20. The patient should be instructed not to brush
the area, but once daily with an antiseptic
mouth rinse (p. 9-1 2) chlorhexidine solution) until 3-6 weeks post-
surgery. Antibiotics may also be used if
appropriate based on the clinician's
judgement.
11. Further Information
Please refer to Straumann website for additional information.

12. Please note
Practitioners must have knowledge of periodontology and instruction in the handling of the Straumann product described herein. The Straumann product is for use in accordance with these instructions for use.

The Straumann product must be used in accordance with the instructions for use provided by the manufacturer. It is the practitioner’s responsibility to use the device in accordance with these instructions for use and to determine if the device fits to the individual patient’s situation.

The Straumann product is part of an overall concept and must be used only in conjunction with the corresponding original components and instruments distributed by Institut Straumann AG, its ultimate parent company and all affiliates or subsidiaries of such parent company (“Straumann”), except if stated otherwise for the respective Straumann product. Use of products made by third parties is not recommended by Straumann, any such use will void any warranty or other obligation, express or implied, of Straumann.

13. Validity
Upon publication of these instructions for use, all previous versions are superseded.

© Institut Straumann AG, 2016. All rights reserved. Straumann® and/or other trademarks and logos shown herein are the trademarks or registered trademarks of Straumann AG and/or its affiliates.

14. Availability
Some versions of the Straumann® regenerative portfolio are not available in all countries.
Deutsch

1. Produktbeschreibung


2. Vorgesehene Verwendung


3. Indikationen

Unsere Studien haben die Wirkung von Endogain® bei der Behandlung von Periimplantitis mit mehr als 6 mm Tiefe und entzündungs- und blutenlosen Zeichen bestätigt. Der Knochenverlust von über 3 mm gelegentlich

Zudem wurde die Wirkung von Endogain® bei der Behandlung von Faktoren, die mit der Entzündung verbunden sind, kontrolliert und nachgewiesen.

4. Kontraindikationen

Basierend auf den Ergebnissen der klinischen Studien ist Endogain® für patienten mit einer aktiven HIV-Infektion, ein kompetentes immunologisches System und Störungen der Blutgerinnung nicht empfohlen.

5. Nebenwirkungen, Wechselwirkungen, Vorsichtsmaßnahmen und mit Straumann-Produkten assoziierte Komplikationen

Einige der häufigsten Nebenwirkungen sind allergische Reaktionen, Schwellungen, Schmerzen und Wundheilungsstörungen.

6. Warningshinweise

Es gibt einige spezifische Anatomien, die auf Dauer und Schwere der Reaktionen bei Patienten mit bestimmten klinischen Situationen hinweisen.

8. Hinweis

Ein spezieller Phasenplan (Erleichterung) von Straumann® Endogain® ist zur Verfügung gestellt. Die Anwendung dieser Phase ist jedoch auf Patienten begrenzt, die eine ausreichende Vorbildung haben sowie auf Patienten, die mit spezifischen Anatomien und Pathologien konfrontiert sind.
9. Verfahren

1. Entnehmen Sie die Medikamente ca. 30 Minuten vor der geplanten Verwendung aus dem Kühlschrank und lassen Sie auf Raumtemperatur zurück.

2. Berücksichtigen Sie die in der Verpackung enthaltene Anleitung.

3. Verwenden Sie die Medikamente innerhalb von 3 Stunden nach erfolgter Injektion der Infusion.

In Verbindung mit einem erweiterten Parodontaltherapieprogramm.

1. Berücksichtigen Sie den geplanten Operationsbereich mittels Leitungsanästhesie oder Sedierung.

2. Vermeiden Sie die Injektion eines Anästhetikums in die Interdentalräume oder in die Marginalgegend.


4. Verwenden Sie die angegebenen Medikamente zur Vermeidung von Komplikationen in der Interdentalzone.

5. Verwenden Sie die Medikamente innerhalb von 3 Stunden nach erfolgter Injektion der Infusion.

6. In Verbindung mit einem erweiterten Parodontaltherapieprogramm.

1. Berücksichtigen Sie den geplanten Operationsbereich mittels Leitungsanästhesie.

2. Vermeiden Sie die Injektion eines Anästhetikums in die Interdentalräume oder in die Marginalgegend.


4. Verwenden Sie die angegebenen Medikamente zur Vermeidung von Komplikationen in der Interdentalzone.

5. Verwenden Sie die Medikamente innerhalb von 3 Stunden nach erfolgter Injektion der Infusion.

6. In Verbindung mit einem erweiterten Parodontaltherapieprogramm.

1. Berücksichtigen Sie den geplanten Operationsbereich mittels Leitungsanästhesie.

2. Vermeiden Sie die Injektion eines Anästhetikums in die Interdentalräume oder in die Marginalgegend.


4. Verwenden Sie die angegebenen Medikamente zur Vermeidung von Komplikationen in der Interdentalzone.

5. Verwenden Sie die Medikamente innerhalb von 3 Stunden nach erfolgter Injektion der Infusion.

6. In Verbindung mit einem erweiterten Parodontaltherapieprogramm.
In Verbindung mit chirurgischen Verfahren zur Optimierung der Weichgewebeverhältnisse:

- In Verbindung mit nicht ausreichend Verfahren zur Optimierung der Weichgewebeverhältnisse kann Endogain® empfohlen werden, um die Weichgewebeverhältnisse in relevanten Bereichen zu optimieren. Der Verband kann nach Bedarf mehrmals über die Verbindungslinie von Knochenimplantaten oder Knochensatzmaterialien verwendet werden.

- Gegebenenfalls kann Endogain® substituiert werden.

- In Verbindung mit Knochentransplantat/Knochenersatzmaterialien: Bei ausgedehnten Defekten oder starken Weichgewebeveränderungen kann StrataRoom® Endogain® empfohlen werden, um die Weichgewebverhältnisse in relevanten Bereichen zu optimieren. Der Verband kann nach Bedarf mehrmals über die Verbindungslinie von Knochenimplantaten oder Knochensatzmaterialien verwendet werden.

- Gesehen wird StrataRoom® Endogain® typischerweise in Verbindung mit Knochentransplantat/Knochenersatzmaterialien und von Knochenimplantaten.

12. Hinweise:

- Zahnärzte müssen über entsprechende Kenntnisse auf dem Gebiet der Pneumologie verfügen und in der Handhabung des in diesem Dokument beschriebenen StrataRoom®-Produktes (StrataRoom®-Produkt) sicher sein, um das StrataRoom®-Produkt sicher und ergonomisch zu verwenden.
- Das StrataRoom®-Produkt muss gemäß den von Hersteller bereitgestellten Gebrauchsanweisung zu verwenden. Es liegt in der Verantwortung des Zahnarztes, das Produkt gemäß Gebrauchsanweisung zu verwenden und in jedem Einzelfall zu prüfen, ob das Produkt für den individuellen Verwendungszweck geeignet ist.

StrataRoom®-Produkte sind Teil eines Gesamtkonzepts und ausschließlich zusammen mit dem entsprechenden logistischen Material und Instrumenten zu verwenden, die von der Institut Straumann AG, ihren Unternehmen oder ihrer entsprechenden Unternehmen oder der Unternehmen oder von Unternehmen, die derartige Produkte herstellen, zur Verfügung gestellt werden. Es liegt in der Verantwortung des Zahnarztes, das Produkt gemäß Gebrauchsanweisung zu verwenden und in jedem Einzelfall zu prüfen, ob das Produkt für den individuellen Verwendungszweck geeignet ist.

13. Gültigkeit


14. Verfügbarkeit

Eigene Artikel des regenerativen Portfolios von Straumann® sind mittlerweile verfügbar. CE-geprüfte Produkte mit dem CE-Zeichen erfüllen die Anforderungen der Medizinprodukte-Richtlinie 93/42/EWG.

LOT Licensed on:

12 Temperaturbereiche (-8°C ~ 36°C ~ 45°C)

Katalognummer

Verfallsdatum


Hersteller
1. Description du produit

Emdogain® est un matériau remplaçable, ressemblant aux surfaces de la dent, qui est mélangé de manière uniforme à une résine comestible et à un adhésif dentaire. Le gel de préparation est appliqué directement sur les surfaces et est ensuite polymérisé sous la lumière intense de la lampe de blanchiment. La surface de la dent est ensuite traitée avec un adhésif dentaire et un couronne est posée. Le produit est ensuite meulé et poli.

2. Utilisation prévue

Emdogain® est indiqué pour la réparation de caries dentaires et la préparation des dents pour l'implantation dentaire. Il est également utilisé pour la réparation des fractures des dents et des pièces de pont dentaire.

3. Indications

- Il est indiqué pour le traitement des caries dentaires et des lésions osseuses.
- Il est également utilisé pour la préparation des dents pour l'implantation dentaire.
- Il peut être utilisé dans le traitement des fractures des dents et des pièces de pont dentaire.

4. Contre-indications

Les contre-indications de l'utilisation des produits Emdogain® ne sont pas spécifiées dans le document fourni. Cependant, il est généralement recommandé de consulter un professionnel de la santé avant de procéder à une intervention dentaire.

5. Effets secondaires, interactions et précautions

Il convient de consulter le manuel d'instructions fourni avec le produit pour obtenir des informations détaillées sur les effets secondaires, interactions et précautions à prendre.

6. Mise en garde

Il est recommandé de bien laver et de bien sécher les dents avant de procéder à l'application du produit. Il est également important de porter des gants lors de l'application du produit pour éviter les risques de contamination.

7. Mise en garde/précautions

- Ne pas utiliser si la brosse de dent est mouillée.
- Ne pas utiliser si la brosse de dent est mouillée et la brosse de dent est mouillée.
- Ne pas utiliser si la brosse de dent est mouillée et la brosse de dent est mouillée.

8. Remarque

La réparation de la surface dentaire utilisant l'adhesive dentaire est une alternative possible à la chirurgie et à la restauration dentaire.

9. Proédure

Le protocole de procédure est décrit dans le manuel d'instructions fourni avec le produit. Il est recommandé de consulter ce manuel avant de commencer l'application du produit.

En conclusion, Emdogain® est un produit efficace pour la réparation de caries dentaires et la préparation des dents pour l'implantation dentaire. Il est également utilisé pour la réparation des fractures des dents et des pièces de pont dentaire.

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**Conjoncture à un labeur répétitif**

La conjoncture à un labeur répétitif consiste en la réalisation de tâches répétitives et monotones. Les tâches répétitives sont celles qui nécessitent une action physique répétée et continue. Elles peuvent être physiques ou intellectuelles. Les tâches répétitives peuvent entraîner des problèmes de santé, tels que des douleurs musculaires ou des troubles de la santé mentale. La conjoncture à un labeur répétitif peut également être source de stress et de burn-out.

**En association avec les procédures de climatisation buccale**

En association avec les procédures de climatisation buccale, le labeur répétitif peut être source de stress et de burn-out. La climatisation buccale est une technique utilisée pour réduire la température de la bouche. Elle peut être utilisée pour faciliter la réalisation d'une tâche ou pour améliorer la confortabilité du patient. Cependant, elle peut également être source de stress et de burn-out si elle est utilisée de manière excessive ou inappropriée.

**Résolution complète de la surface radiculaire**

La résolution complète de la surface radiculaire peut être réalisée par un procédé de climatisation buccale. Ce procédé consiste à appliquer un gel de climatisation buccale sur la surface radiculaire et à laisser agir pendant une certaine durée. La climatisation buccale peut être utilisée pour faciliter la réalisation d'une tâche ou pour améliorer la confortabilité du patient.
pour les lèvres fermées stables. Toute pression ne doit être exercée que sur le bandeau après la suture. Le patient doit être d'abord nettoyé pour être fixé dans la zone opératoire, mais sans interaction avec le nez de la bouche antérieurement avec un système de fixation antérieurement avec un système de fixation antérieur.

- La suture est entièrement indiquée et les sutures ne participant pas plus à la stabilité de la plaie.

En association avec un matériel de greffe osseuse :

- En cas de défauts importants ou si le soutien des tissus mous est souhaité, Straumann® Endogain® peut être utilisé en association avec un matériel de greffe osseuse.

- En association avec une greffe osseuse, Straumann® Endogain® est ajouté goutte à goutte au substitut osseux et le produit qui en résulte est mélangé avec une pâte ou d'autres instruments permettant d'effectuer un mélange jusqu'à ce que le mélange soit un composant homogène stable à température auditive de l'inactivation.

- Le défaut doit être rempli complètement et sans défaut de l'enduit résultat. Une suraugmentation doit être évitée. La greffe osseuse doit être complétée en douceur dans le défaut d'assurer une stabilité incisive correcte et le maintien de l'os et de la tissu dentaire.

- Une couche de Straumann® Endogain® est appliquée à la surface de la plaque avant l'application de la plaque de greffe osseuse et le mélange de greffe osseuse Straumann® Endogain® doit être appliqué sur la surface de la plaque avant l'application de la plaque de greffe osseuse et le mélange de greffe osseuse Straumann® Endogain® peut être appliqué sur la surface de la plaque avant l'application de la plaque de greffe osseuse Straumann® Endogain®.

12. Remarque

Les patients doivent avoir acquis les connaissances en paramédicale et la formation nécessaire à la manipulation du produit Straumann® décrit dans le présent document (« Produits Straumann »), afin d'utiliser le matériel de greffe osseuse et toute sécurité en matière de plaie, conformément au mode d'emploi et la consigne de sécurité qui est fourni par le fabricant et à l'attention du praticien. Le produit doit être utilisé conformément au mode d'emploi fourni par le fabricant.

13. Validité

Le produit est mis sur le marché selon la réglementation applicable et est conçu pour un usage humain à l'attention du praticien et de l'opérateur. Il est utilisé conformément au mode d'emploi et la consigne de sécurité qui est fourni par le fabricant.

14. Disponibilité

Certains articles de la gamme Straumann® sont disponibles dans les pharmacies et distributeurs de matériel dentaire autorisés par Straumann AG et ses filiales.
1. Descrizione del prodotto

SurgicalEndos® Endogain® è un materiale ristabilibile impiantabile che supporta la formazione e l’ossigenazione del tessuto parenchimale. Ha un processo di riattivazione che inizia in opposizione con il tessuto che lo circonda.

1.1. Indicazioni

- Endogain® utilizzato nei deficit di osso necessari che hanno mostrato di offrire una migliore riparazione radicale rispetto alla tecnica per la rimozione di tessuto avan- 
a. Il grado di riattivazione del tessuto avviene di solito immediatamente dopo l'apporto, quindi è adatto per usi che richiedono rapidità e affidabilità.
- Endogain® è indicato per supportare la riparazione e la rigenerazione del tessuto osseo, in particolare per interventi di chirurgia allineamento.

4. Contraindicationi

Sia la base dei risultati dell’analisi del rischio, la seguente popolazione di pazienti è proibita:
- pazienti con ipermetabolismo del tessuto osseo, in particolare per interventi di chirurgia allineamento;
- pazienti con deficit di osso necessari che hanno mostrato di offrire una migliore riparazione radicale rispetto alla tecnica per la rimozione di tessuto avanzato.

7. Attenzione/Precauzioni

- Non utilizzare se la confusione o il desiderio sono a danne.
- Se alla confusione o il desiderio sono a danne.

8. Nota

- SurgicalEndos® Endogain® può essere utilizzato in setacci con o senza siringhe, ma in ogni caso di siringa deve essere utilizzato su un solo paziente.

9. Procedura

1.1. Impiego di Endogain® in pazienti con deficit di osso necessari che hanno mostrato di offrire una migliore riparazione radicale rispetto alla tecnica per la rimozione di tessuto avanzato.

1.2. Utilizzo di Endogain® con siringhe e con siringhe con Endogain®.

1.3. Utilizzare Endogain® con ca. 1 g, gestando eventualmente il rimanente.

Associazioni a chiusura parziale convessione

1. Aste in osso che intercettano il modello di riferimento.

2. Praticare incisioni per intercettazione.

3. Praticare incisioni per intercettazione.
Associazioni e procedure chirurgiche orali per migliorare la guarigione di ferite dei tessuti molli:

1. Associazioni a livello di chirurgia orale per migliorare la guarigione dei tessuti molli. 

2. Prima della chirurgia orale, il paziente deve essere attentamente informato sulle procedure e sulle conseguenze.

3. Il chirurgo deve essere competente nelle procedure chirurgiche orali.

4. Il paziente deve essere informato sulla necessità di follow-up postoperatorio.

5. Il paziente deve essere informato sulla possibilità di complicanze e delle misure da attuare in caso di emergenza.


7. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

8. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.


10. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

11. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

12. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

Associazioni a materiale per interno osseo:

1. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

2. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

3. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

4. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

5. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

6. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

7. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

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11. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

12. Il paziente deve essere informato sulla necessità di fare attenzione ai sintomi che potrebbero essere evidenziati.

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14. Disponibilità
Alcuni articoli della linea Straumann® regenerative non sono disponibili in tutti i paesi.

15. Fase di guadagno
Fare riferimento alle specifiche procedure riportate alla sezione V.

16. Ulteriori informazioni
Per ulteriori informazioni consultare il sito web Straumann.

12. Importante
È necessario che l'utilizzatore presente prodotto Straumann® ("Prodotto Straumann") conosca e si riferisca a tutte le istruzioni per l'uso fornite dal produttore. È responsabilità dell'utilizzatore utilizzare il dispositivo in conformità con le presenti istruzioni per l'uso. La non conformità a queste istruzioni può comportare danni anche gravi per la persona che utilizza il dispositivo.

Il prodotto Straumann è un prodotto del gruppo Straumann, che fornisce prodotti e servizi per la chirurgia ossea e periodontale, e si riferisce a tutti i prodotti e servizi offerti da Straumann. È responsabilità dell'utilizzatore utilizzare il dispositivo in conformità con le presenti istruzioni per l'uso. La non conformità a queste istruzioni può comportare danni anche gravi per la persona che utilizza il dispositivo.

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Instrucciones de uso: Straumann® Endogain®

1. Descripción del producto

Endogain® es un material compuesto que favorece la regeneración periodontal y que permite la creación de tejido de soporte óseo sustituo en defectos de la inserción del hueso.

2. Uso previo

El uso de Endogain® está indicado para la reparación tisular de tejido de soporte óseo en defectos de inserción periodontal y en defectos de inserción del hueso.

3. Indicaciones

- Endogain® se utiliza en defectos de recesión gingival que demandan la colocación de una cubierta o protección de tejido gingival.
- Endogain® se utiliza en defectos de inserción periodontal y en defectos de inserción del hueso.

4. Contraindicaciones

- No se utiliza en defectos de recesión gingival que no demanden la colocación de una cubierta o protección de tejido gingival.

5. Efectos secundarios, interacciones y precauciones

- No se han reportado efectos secundarios con el uso de Endogain®.
- Se recomienda que los pacientes utilicen hilo dental después del procedimiento.

6. Advertencias

- Se debe informar a los pacientes sobre la importancia de la higiene dental después del procedimiento.

7. AtenCIÓN/PrecAUCiones

- No se utiliza en defectos de recesión gingival que no demanden la colocación de una cubierta o protección de tejido gingival.

8. Notas

- La separación de Endogain® se realiza mediante incisión en la piel para separar el tejido durante el procedimiento.

9. Procedimiento

- El procedimiento se realiza mediante incisión en la piel para separar el tejido durante el procedimiento.

En combinación con cirugía perióntal y convencional.

- Se debe informar a los pacientes sobre la importancia de la higiene dental después del procedimiento.
7. El bisección de los nervios superficiales puede facilitar la reducción del dolor.
8. Las suturas pueden retirarse cuando los colgajos y la interfaz interfaz por lo menos están establecidos, normalmente al cabo de 2-3 semanas. Después de reponer la inyección de anestesia local con una inyección de suero fisiológico en las papilas interdentes, se aplican apósitos.
9. Juntamente con colgajo coronal avanzado para el tratamiento de defectos tipo recesión:
   a) Ancelar la cono o del diente con una pieza superpuesta con el diente adyacente para el colgajo coronal avanzado.
   b) Juntamente con colgajo de la cara labial para la recesión del hueso.

Con procedimientos quirúrgicos orales para mejorar la cicatrización de los tejidos blandos:
- Con procedimientos quirúrgicos orales para mejorar la cicatrización de los tejidos blandos.
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Protocol Version 5.0, 29-Mar-2018
- Las suturas se levan cuando la cicatrización emerge del colgajo. Establece las suturas y no aportan estabilidad a la herida.

**Junto con material de inyección ósea:**
- En caso de defectos excesivos cuando se desee soporte de los tejidos blandos, Straumann® EndoLogix® se puede utilizar junto con un material de tejido duro.
- Cuando se combina con materiales de injerto ósea, Straumann® EndoLogix® se añade guía a cada sus injertos óseos y el producto resultante se suministra con una espátula de otro instrumento adecuado para la mezcla hasta que se vuelva pastosa de consistencia parecida a la de la base de una pasta para la proección de la corona.
- El defecto debe ser rellenado completamente con la mezcla del material. Debería existir un aumento no excesivo. El injerto óseo debe completarse firme y duradero en el defecto para garantizar la estabilidad mecánica frente a la compresión. Debe evitar una presión excesiva que pueda provocar el aplastamiento de las particulas de la mezcla de la mezcla.
- Para mejorar la cicatrización de la herida en el tejido blando, se aplica una capa de Straumann® EndoLogix® en la parte superior del injerto óseo inmediatamente antes de la sutura definitiva de la herida.
- En caso de tratamiento de la superficie radiográfica perióntal Straumann® EndoLogix® puede aplicarse sobre la superficie radiográfica antes de la aplicación del injerto óseo de la mezcla del defecto óseo Straumann® EndoLogix® para garantizar una cobertura adecuada de la superficie radiográfica con Straumann® EndoLogix®.

**13. Validez**
La publicación de estas instrucciones de uso reemplaza la anulación de todas sus versiones anteriores.

**Referencia**
- Straumann AG, 2016. Todos los derechos reservados.
- Straumann® y otras marcas y logotipos de Straumann® aquí mencionados son marcas comerciales o marcas registradas de Straumann Holding AG y sus filiales.

**14. Disponibilidad**
Algunos artículos de la línea Straumann® Regenerative no están disponibles en todos los países.

**CE**
- Los productos Straumann son marcas CE y cumplen los requisitos de la Directiva relativa a productos con marca CE (93/42/EEC).

**LOT**
- Código de fecha

**L1**
- Limitaciones de temperatura
  - (3°C a 38°C)

**REF**
- Número del catálogo

**Fecha de caducidad**
- Consulte, consulte, consulte, consulte, consulte.

**Precaución, consulte, consulte, consulte, consulte,**
- La pretensión mediante técnicas de prensamiento ópticas,
- No realizar,
- Fabricante,
- Consulte, consulte, consulte, consulte, consulte.
Português

Instruções de utilização: Straumann® Endogain®

1. Descrição do produto
O Straumann® Endogain® é um material implantável, multifacetado que promove a regeneração periodontal ao acelerar a ausência da doença dos solenoides. O Endogain® é constituído por proteínas e aminoglicósidos de matriz do estroma vascular do tecido em desenvolvimento de origem virulentes, num modelo de alginato de pectina. O gel contém proteínas da matriz extracelular (ECM) e é indicado para a regeneração periodontal.

2. Instruções de utilização
O Endogain® deve ser aplicado soba a presença de tecido de matriz da ECM, como fibras de colágeno, a partir de um dispositivo de aplicação. O dispositivo deve ser introduzido na fenda de um implante ou na cavidade periodontal.

3. Indicações
- O Endogain® está indicado para a regeneração periodontal.

4. Contra-indicações
- O Endogain® não deve ser aplicado em situações de infecção ou hiperatividade do sistema imunológico.

5. Efeitos secundários, interações e precauções

6. Advertências
- Os estudos clínicos indicam que o Endogain® pode ser usado em casos de regeneração periodontal.

7. Cuidados/Precaveções
- O Endogain® deve ser armazenado em um local fresco e seco.

8. Nota
- É importante seguir as instruções do fabricante para evitar complicações.

9. Procedimento
- O Endogain® deve ser aplicado em uma fenda de implante ou cavidade periodontal.

10. Conclusão
- O Endogain® é um material de regeneração periodontal eficaz e seguro, comprovado em estudos clínicos.

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4. Aplique imediatamente o imódgan* sobre as superfícies expostas das facas, começando pelo nível mais apático do tecido. Aplique o imódgan* até cobrir totalmente as áreas expostas da superfície dos tecidos. (Duração: 5 minutos). Se necessário, é possível que seja necessário de novo se o tecido estiver seco.

5. É recomendável que a rotação da área temporária seja feita com uma rotação de 90º para evitar erosão secundária da superfície da faca. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).

6. O paciente deve ser alertado lá o bocal diretamente com um titirica de borracha, a goma, que deve ser aplicado na superfície da superfície dos tecidos. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).

7. O paciente deve ser alertado lá o bocal diretamente com um titirica de borracha, a goma, que deve ser aplicado na superfície da superfície dos tecidos. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).

8. As suturas podem ser retiradas quando as alças e o interior da área do tecido estiverem suficientemente suturadas. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).

9. As suturas de cabeça de fio trípode e de cabeça de fio trípode podem ser retiradas quando as alças e o interior da área do tecido estiverem suficientemente suturadas. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).

10. As suturas de cabeça de fio trípode e de cabeça de fio trípode podem ser retiradas quando as alças e o interior da área do tecido estiverem suficientemente suturadas. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).

11. As suturas de cabeça de fio trípode e de cabeça de fio trípode podem ser retiradas quando as alças e o interior da área do tecido estiverem suficientemente suturadas. Deve-se tomar o cuidado de não deixar o solo exposto à superfície da superfície dos tecidos. (Duração: 5 minutos).
10. Fase de cicatrização
Consulte a parte referente ao procedimento específico da secção 9.

11. Outras informações
Consulte a página da Straumann na Internet para mais informações.

12. Atenção
Os médicos devem ler o estudo e a instrução antes de utilizar o sistema. O sistema de tratamento deve ser usado como instruído para obter os efeitos desejados. O estudo é indicado para uso em humanos e deve ser cuidadosamente monitorado.

O estudo é indicado para uso em humanos e deve ser cuidadosamente monitorado.

Caso qualquer monitoramento esteja ausente, deve-se consultar um médico.

13. Garantia
Os produtos da Straumann têm garantia de qualidade e segurança.

14. Disponibilidade
Os produtos da Straumann estão disponíveis em todas as lojas.

Nota: Este documento é uma tradução do original em português. Para obter informações mais detalhadas, é recomendado consultar o original em português.
Appendix 3 – Instructions For Use IFU 700096 - Pref-Gel®

Gebrauchsanweisung: Straumann® PrefGel 0,6 ml
Instructions for use: Straumann® PrefGel 0,6 ml
Mode d’emploi: Straumann® PrefGel 0,6 ml
Istruzioni per l’uso: Straumann® PrefGel 0,6 ml
Instrucciones de uso: Straumann® PrefGel 0,6 ml
Instruções de utilização: Straumann® PrefGel 0,6 ml
Bruksanvisning: Straumann® PrefGel 0,6 ml
Gebruiksanwijzing: Straumann® PrefGel 0,6 ml
Brugsanvisning: Straumann® PrefGel 0,6 ml

Инструкции по применению. Straumann® PrefGel 0,6 мл

Hersteller / Manufacturer / Fabricant / Produttore / Fabricante / Fabricante / Tillverkare / Producer / Изготовитель

Institut Straumann AG, CH-4002 Basel/Switzerland, www.Straumann.com
Caution: U.S. Federal law restricts this device to sale by or on the order of a dental professional.

1. Product Description
Straumann® PrefGel is a neutral EDTA formulation intended for topical application onto exposed root surfaces during periodontal surgery in order to remove the smear-layer. Mechanical debridement of a root surface inevitably produces a smear-layer, which in turn may prevent or retard periodontal healing. Exposure of collagen fibers may be important for linking fibrin in the blood clot to the root surface. Clinical studies with PrefGel® have demonstrated the ability to remove the smear-layer and to expose the collagenous matrix of dentin surfaces.

The package contains 5 syringes Straumann® PrefGel 0.6 ml edetate disodium [EDTA] 2 H₂O 24% neutral in carboxymethyl cellulose (CMC) gel and 5 application needles.

2. Intended use
Straumann® PrefGel is intended for topical application onto exposed root surfaces during periodontal surgery in order to remove the smear layer.

3. Indications
- PrefGel® has been shown to effectively remove the smear-layer. PrefGel® has also been shown to produce a fibrillar collagenous meshwork on the exposed and conditioned root surface by selective removal of mineral.

4. Contraindications
No contraindications are currently identified for this medical product.

5. Side effects, interactions and precautions; complications with Straumann products
- PrefGel® does not induce any detectable necrosis in the surrounding periodontal tissues.
- PrefGel® has been well tolerated in clinical studies.
- Reversible and short duration procedure-related dentin hypersensitivity may occasionally occur.

6. Warnings
No warnings are currently identified for this medical product.

7. Caution/Precautions
- Do not use if sterile package is opened or damaged.
- To prevent possible cross contamination discard or return damaged package and the enclosed device.
- Syringe and application device are single use items. Do not re-sterilize or re-use. Re-use of single-use devices creates a potential risk of patient or user infection. Contamination of the device may lead to injury or serious illness of the patient.
- Each prefilled syringe is intended for use in one patient only.
- Straumann® PrefGel must be stored at 2–8°C / 36–46°F upon receipt.
- Be aware that bending the needle may cause breakage.

8. Procedure
1. Remove PrefGel® from cold storage approx. 30 minutes before use and allow it to assume ambient temperature.
2. Remove the plastic top of the syringe.
3. Carefully attach the supplied application needle.
4. After application, discard any residual gel, the syringe and needle per local protocol.
Periodontal surgery:
1. Following reflection of mucoperiosteal flaps in the area selected for periodontal surgery, the exposed root surfaces are mechanically debrided in order to remove any remaining plaque and/or calculus.
2. PrefGel™ is then topically applied onto the exposed and debrided root surfaces for 2 minutes. Only apply PrefGel™ onto those parts of the root surfaces which will be covered by soft tissues once flaps are replaced and sutured. Active rubbing (“burnishing”) is not recommended.
3. After conditioning, the root surfaces must be rinsed thoroughly with sterile saline.
4. Care should be taken to avoid re-contamination of the conditioned root surfaces after the final rinse and prior to treatment with regenerative topical products (e.g. Straumann® Emdogain).

9. Further Information
Please refer to the Straumann website for additional information.

10. Please Note
Practitioners must have knowledge of periodontal therapy and instruction in the handling of the Straumann product described herein ("Straumann Product") for using the Straumann Product safely and properly in accordance with these instructions for use.

The Straumann Product must be used in accordance with the instructions for use provided by the manufacturer. It is the practitioner's responsibility to use the device in accordance with these instructions for use and to determine if the device is suitable for the individual patient situation.

The Straumann Product is part of an overall concept and must be used only in conjunction with the corresponding original components and instruments distributed by Institut Straumann AG, its ultimate parent company and all affiliates or subsidiaries of such parent company ("Straumann"). Use of products made by third parties, which are not distributed by Straumann, will void any warranty or other obligation, express or implied, of Straumann.

11. Validity
Upon publication of these instructions for use, all previous versions are superseded.

© Institut Straumann AG, 2012. All rights reserved.
Straumann® and/or other trademarks and logos from Straumann® mentioned herein are the trademarks or registered trademarks of Straumann Holding AG and/or its affiliates.

12. Availability
Some items of the Straumann® regenerative portfolio are not available in all countries.
Straumann Produkte mit dem CE-Zeichen erfüllen die Anforderungen der Medizin-
geräte-Richtlinie 93/42 EGW / Straumann Products with the CE mark fulfill the requirements of the Medical Devices
Directive 93/42 EEC / Les produits Straumann portant la marque CE sont conformes à la Directive
93/42 EEC relative au matériel médical / I prodotti Straumann provvisti di marchio CE soddisfano i requisiti della Direttiva sui
Prodotti Medici 93/42 CEE / Los productos Straumann con el sello CE cumplen los requisitos de la directiva
sobre productos médicos 93/42 CEE /

Chargennummer / Batch code / Numéro de lot / Numero di lotto / Código de lote

Temperature limitation (2 °C-8 °C / 36 °F-46 °F)

Katalognummer / Catalogue number / Référence du catalogue / Numero di
catalogo / Número de catálogo

Verfallsdatum / Use by date / Date limite d'utilisation / Usare entro / Fecha de
caducidad

Vorsicht, Begleitdokumente beachten / Caution, consult accompanying
documents / Attention, lire les documents joints / Attenzione, consultare i documenti
di accompagnamento / Atención, consultar la documentación adjunta

Sterilisiert anhand aseptischer Techniken / Sterilized using aseptic processing
techniques / Sterilisé en utilisant des techniques aseptisées / Sterilizzato utilizzando
techniche asettiche / Esterilizado mediante técnicas de proceso asépticas

Nicht wiederverwenden / Do not reuse / Ne pas réutiliser / Non riutilizzare / No
reutilizable

Rx only

Caution: U.S. Federal law restricts this device to sale by or on the order of a dental
professional.

Hersteller / Manufacturer / Fabricant / Produttore / Fabricante
Appendix 3 – Treatment Workflow

Initial Exam, Periodontal status

Max 2 weeks

Anesthesia

Minimally invasive scaling and root planing

Control bleeding

Use hand/diamond/ultrasonic scalers
No lasers

Prohibit vasoconstrictors and hemostatic agents at the time of Emdogain application

PrefGel 2 min

Irrigate with sterile saline thoroughly

EMDOGAIN

2-3 weeks

Oral hygiene

Starting apically and advancing coronally

Chlorhexidine 1 week, with no brushing
Soft brush, 90° angle
No flossing or waterpik 1 month
No local or systemic antibiotics
Supragingival plaque removal at low power settings

No anesthesia
Deplaque to level curette enters the defect

EMDOGAIN

Starting apically and advancing coronally
No EDTA / PrefGel

Chlorhexidine 1 week, with no brushing
Soft brush, 90° angle
No flossing or waterpik 1 month
No local or systemic antibiotics

1 month

Periomaintenance

3, 6, 9, 12 months

Reevaluation visits
Appendix 4 – Visual Analog Scale (VAS)

<table>
<thead>
<tr>
<th>Subject Initials</th>
<th>1-2 Days after Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject ID.</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td></td>
</tr>
</tbody>
</table>

Instructions:
To be completed by the patient
Complete this page 1 to 2 days after treatment.
Indicate the level of pain in the area of your mouth treated for the study.
Please mark the lines as instructed below.

**RIGHT side of mouth**

Please mark your pain level by drawing one vertical mark through the line below.

No pain  __________________________  Worst pain possible

**LEFT side of mouth**

Please mark your pain level by drawing one vertical mark through the line below.

No pain  __________________________  Worst pain possible
<table>
<thead>
<tr>
<th>STRAUMANN</th>
<th>SUBJEC T INTAKE</th>
<th>1 Week after Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR 01/15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Instructions:**
- To be completed by the patient.
- Complete this page 1 week after treatment.
- Indicate the level of pain in the area of your mouth treated for the study.
- Please mark the lines as instructed below.

### RIGHT side of mouth
Please mark your pain level by drawing one vertical mark through the line below.

- No pain

### LEFT side of mouth
Please mark your pain level by drawing one vertical mark through the line below.

- No pain
<table>
<thead>
<tr>
<th>Subject Ints:</th>
<th></th>
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**Instructions:**
To be completed by the patient.
Complete this page 2 weeks after treatment.
Indicate the level of pain in the area of your mouth treated for the study.
Please mark the lines as instructed below.

**RIGHT side of mouth**
Please mark your pain level by drawing one vertical mark through the line below.

No pain                                   Worst pain possible

**LEFT side of mouth**
Please mark your pain level by drawing one vertical mark through the line below.

No pain                                   Worst pain possible
Appendix 5 – Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

Protocol Version 5.0, 26-Mar-2018
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse
events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and where appropriate, made publicly available.