CR 03/13

A randomized controlled clinical trial to investigate the capability of *Straumann® VivOss™* compared to *Geistlich Bio-Oss®* in sinus floor augmentation.

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Protocol reviewed and approved by:

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Synopsis

Study Title:	A randomized controlled clinical trial to investigate the capability of *Straumann® VivOss™* compared to *Geistlich Bio-Oss®* in sinus floor augmentation.
Protocol Code:	CR 03/13
Objective	To demonstrate superiority of *Straumann® VivOss™* compared to *Geistlich Bio-Oss®* in regards to the ratio of newly formed bone to residual bone substitute.
Study Design:	A prospective, randomized, controlled, open label study.
Subject Population:	**Inclusion Criteria** 1. Subject must have voluntarily signed the informed consent before any study related action 2. Males and females with at least 18 years of age (including 18 years) 3. Subject needs augmentation procedure in the sinus to prepare for implant placement. 4. Subject must have a residual bone height of 2 to 4 mm. 5. Adequate oral hygiene ((Full mouth plaque index (O'Leary, et al. 1972) <25%) at baseline 6. Adequate control of inflammation ((full mouth bleeding on probing (Ainamo and Bay 1975)) ≤25% at baseline **Exclusion Criteria** Pre-surgical exclusion criteria 1. Systemic disease that would interfere with bone or wound healing and dental implant therapy (e.g. uncontrolled diabetes) 2. Any contraindications for general bone grafting and oral surgical procedures 3. Any anomalies of the sinus that could interfere with planned procedures 4. History of local irradiation therapy 5. Local inflammation, including untreated periodontitis 6. Medical conditions requiring chronic high dose steroid therapy 7. Treatment with an investigational drug or device within a 30 day period immediately prior to surgery at visit 2, or expected participation in any other investigational drug or device study during the conduct of this trial.

	8. Antibiotic treatment or anti-inflammatory treatment within 4 weeks prior to surgery 9. History of alcoholism or drug abuse 10. Immunocompromised subjects 11. Subjects who smoke >10 cigarettes per day or tobacco equivalents or chew tobacco 12. Conditions or circumstances, in the opinion of the investigator, which would prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance or unreliability 13. Physical or mental disabilities that would interfere with the ability to perform adequate oral hygiene 14. Current pregnancy (pregnancy test) and breastfeeding women Secondary exclusion criteria at or after surgery 1. Defects of the Schneider Membrane
Treatment Plan:	• **Visit 0 (Informed Consent, 2 to 14 days before screening):** signing informed consent after informed consent process. • **Visit 1 (Screening):** pregnancy test (only if female with childbearing potential), demographic data, medical/dental history, inclusion/exclusion criteria, planned implant site, CBCT (not older than 12 months) • **Visit 2 (Sinus elevation):** adverse events, concomitant medication, randomization, details of surgery, secondary exclusion criteria, intra-oral photographs • **Visit 3 (wound healing assessment):** adverse events, concomitant medication, suture removal, post-operative wound healing control, intra-oral photographs • **Visit 4 (Implant placement / Histology):** adverse events, concomitant medication, histology sampling, dental implant placement, intra-oral photographs • **Visit 5 (wound healing assessment):** adverse events, concomitant medication, suture removal, post-operative wound healing control, intra-oral photographs • **Visit 6 (Initial implant loading):** adverse events, concomitant medication, survival of the dental implant, success of the dental implant, intra-oral photographs, periapical x-ray
Primary Endpoint:	The histological evaluation of the ratio of newly formed bone to residual bone graft in *Straumann® VivOss™* compared to *Geistlich BioOss®* at visit 4 (6 month ± 7 days, after sinus elevation).
Secondary Endpoints:	• Survival rate of study implants evaluated at visit 6 (Initial implant loading) • Success rate of study implants evaluated at visit 6 (Initial implant loading)

Study Device(s):	**Test:** Synthetic biphasic calcium phosphate (HA/TCP 10:90) *Straumann® VivOss™* **Comparator:** Demineralized bovine bone mineral (*Geistlich Bio-Oss®*)
Safety:	The subjects will be monitored continuously for adverse events by the investigators.
Registration Status:	All products are CE marked
Study Duration:	The total study duration for each subject should be 9-14 months from screening to last visit.
Number of participating Centres:	Two centres
Number of subjects planned to be enrolled:	50 subjects (25 in the test group, 25 in the comparator group)
Sponsor:	Institut Straumann AG Peter Merian-Weg 12 CH-4002 Basel Switzerland
Investigators:	Dr. Ronald E. Jung, Zurich (Switzerland) Dr. Dr. Andres Stricker, Constance (Germany)
Compliance:	This study and any amendments will be performed according to ISO 14155 (Second Edition, 2011-02-01) and conform to the Declaration of Helsinki (last revised Seoul 2008) and local legal and regulatory requirements.

Schedule of Assessment

Tasks	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Informed Consent	Screening Visit	Sinus elevation (Baseline)	Wound healing assessment	Implant placement	Wound healing assessment	Initial implant loading
	28-2 days before screening	14-0 days before Baseline	Day 0	Day 7-14	6 months ± 7 days	7-14 days after visit 4	4 months ± 1 month after visit 4
Informed Consent	X						
If female, pregnancy test		X					
Demographics (date of birth, gender, ethnic origin)		X					
Medical & Dental History		X					
Inclusion /Exclusion Criteria		X					
Planned implant site		X					
Cone Beam CT (CBCT)		X*1, *2					
Adverse events			X	X	X	X	X
Concomitant medication		X	X	X	X	X	X
Randomization			X				
Augmentation			X				
Secondary inclusion criteria			X				
Intra-oral Photographs			X	X	X	X	X
Suture Removal				X		X	
Implant Placement					X		
Bone Biopsy					X		
Wound healing assessment				X		X	
Periapical x-ray							X*2
Implant survival							X
Implant success							X

*1 If an CBCT was taken up to 12 months in advance to the baseline visit (visit 2) there is no need to take a new CBCT.

*2 Radiographs should only be taken if clinically necessary.

Abbreviations:

Ø	Diameter
AE	Adverse Event
BoP	Bleeding on Probing
CBCT	Cone Beam Computed Tomography
CE	Communauté Européenne (Marking of registered device in Europe)
CRF	Case Report Form
FDI	Fédération Dentaire Internationale
FMPPD	Full Mouth Probing Pocket Depth
FU	Follow-up
GBR	Guided Bone Regeneration
GCP	Good Clinical Practice
HA	Hydroxyapatite
IA	Interim Analysis
ICF	Informed Consent Form
ID	Identity
IEC	Independent Ethics Committee
ISO	International Organization for Standardization
mm	Millimetre
µm	Micrometer
N	Number
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Study Day
STL	Soft Tissue Level
TCP	Tri-Calcium-Phosphate
USADE	Unanticipated Serious Adverse Device Effect

1 Table of Contents

2 Background and Rationale

Maxillary sinus floor elevation to allow the placement of endosseous implants has become a standard surgical procedure in the last decades with reliable long-term results, both in clinical [1,2,3] and experimental studies.[4,5,6,7,8]

Bone grafting procedures have been shown to be predictable methods for augmenting the bone volume in areas with deficient bone quantity or quality in order to allow dental implant insertion according to planned prosthetic position.

Autogenous bone grafts (autografts) have been recommended to be used in order to act as an osteoinductive and osteoconductive scaffold.[9] The material is harvested at intraoral or extraoral sites.[10] The successful use of autogenous bone as bone void filler has made this material the standard as it has already been for bone reconstructive surgery in orthopedics. Nevertheless, this material has a number of disadvantages. Most importantly, the necessity for a second site to harvest the autogenous bone increases the duration of the surgical intervention, the surgical risk as well as post-surgical morbidity at harvesting site. In order to avoid the drawbacks of this material, bone graft substitutes have been proposed. These can be classified in the following groups: allografts (from same species (human), but different individual), xenografts (from different species, usually animal derived from bovine origin) and alloplast (synthetic origin). They have been shown to be effective and have demonstrated a high implant success rate, but much controversy still exists regarding the capability of these materials to be resorbed and substituted by newly formed bone to allow adequate osseointegration of dental implants.

Bio-Oss®, a deproteinized bovine bone mineral, is one of the most commonly used and evidence-based bone substitute materials in the field of dental surgery.[11] Pre-clinical[12] and clinical studies[13] have shown that Bio-Oss® can preserve bone dimensions adequately. The combination of Bio-Oss® and the resorbable collagen membrane Bio-Gide® has been found to be effective for bone regeneration in situations where dental implants are placed.[14 ,15]

Studies have shown that the biphasic calcium phosphate (BCP) Straumann BoneCeramic® used for sinus floor elevations or alveolar ridge preservation can result similar bone changes to standard graft material (Bio-Oss®), [16,17] and can result in excellent survival and success rates of dental implants placed subsequently[18]. Straumann BoneCeramic® consists of hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP) in a 60:40 ratio, so that the HA acts as a scaffold for space maintenance while the β-TCP resorbs and supports bone regeneration. A new second generation macro- and microporous BCP (mean micropore diameter 1 µm) has been developed with an HA/TCP ratio of 10:90 and controlled microporosity, which may be an important factor in the osteoconductive capacity of calcium phosphate ceramics.[19] This material has demonstrated biocompatibility and osteoconductivity[20,21] and is designed to act as a scaffold that allows cells to infiltrate the site of the defect for subsequent bone regeneration and is designed to provide substitute degradation, i.e. chemical/non-cellular dissolution of BCP in parallel with resorption by osteoclasts. Bone formation starts with an organic cellular matrix being formed by cells (including pre-osteoblasts) around the BCP particles. Preclinical data have indicated that in addition to direct bone deposition on the surface of the BCP particles, mineralization and ossification also occurs in the inter-granular spaces. This occurs as a result of calcium and phosphate, released by substitute degradation, that become embedded in the organic matrix,

similar to the process of ossification that occurs during osteogenesis; this is assumed to enable random bone formation throughout the defect.

3 Study Endpoints

3.1 Primary Endpoint

- To histologically evaluate the ratio of newly formed bone to residual bone graft in *Straumann® VivOss™* compared to *Geistlich Bio-Oss®* at 6 months (± 1 7 days) after sinus floor augmentation.

3.2 Secondary Endpoints

- Survival rate of study implants evaluated at visit 6 (Initial implant loading)
- Success rate of study implants evaluated at visit 6 (Initial implant loading)
  Crestal bone level loss as well as the criteria according to Buser *et al.* will be used to define the survival and success rate of study implants.

4 Study Design

4.1 Type and Design of Study

This is a prospective, randomized, controlled, open label study, conducted at two sites in Germany and Switzerland comparing two treatment groups.

4.2 Indications for use

The package inserts (instructions for use) provide detailed information and instructions for the usage of the investigational bone substitute material and membrane as well as for the comparator products.

All used products are CE marked.

4.3 Study Treatments

Before entering into the study, each subject has to sign an informed consent. A subject is enrolled if she/he meets all inclusion criteria and at the same time does not meet any exclusion criteria. Enrolled subjects will be scheduled for sinus elevation. At surgery subject eligibility will again be evaluated according to secondary exclusion criteria. Subjects who do not meet any secondary exclusion criteria are randomized to one of the following groups:

a) Sinus floor elevation with *Straumann® VivOss™*
b) Sinus floor elevation with *Geistlich Bio-Oss®*

After a healing time of 1-2 weeks, sutures are removed, and the wound healing is evaluated. After a healing time of 6 months, an intermediate osteotomy for the dental implant placement is done by means of a trephine burr in such a way that the biopsy is harvested at the same time. Dental implant placement will be completed according to the standard procedure of the clinic. After a healing time of 1-2 weeks, the sutures are removed and the wound healing is evaluated. 4 months after implant placement the implant is initially loaded and the survival as well as the success rate will be evaluated.

4.4 Number of Subjects

This study will be performed in two clinical centres, one in Germany and one in Switzerland; these centres are expected to recruit 50 subjects in total, 25 subjects in test group, 25 subjects in control. Planned subject recruitment period is 3 months. The recruitment is competitive. Recruitment will be stopped as soon as recruitment is complete.

4.5 Study Duration

The primary endpoint will be assessed 6 months ± 7 days after sinus floor elevation. The entire study duration for each enrolled subjects is 9-14 months (screening to last visit).

The entire study duration from first patient in until last patient out will be approximately 17 months.

5 Study Population

Generally healthy female and male subjects, who are at least 18 years of age and are willing to participate in this study and who would benefit from a prosthetic reconstruction with a dental implant but need a sinus floor elevation in either one or both sinuses.

5.1 Inclusion Criteria

The subjects will be evaluated for initial study eligibility during the screening visit. Those subjects who appear eligible according to the inclusion/exclusion criteria will be asked to sign an informed consent form to be enrolled into the study. The following criteria must be met for inclusion in the study:

1. Subject must have voluntarily signed the informed consent before any study related action
2. Males and females with at least 18 years of age (including 18 years)
3. Subject needs augmentation procedure in the sinus to prepare for implant placement.
4. Subject must have a residual bone height of 2 to 4 mm.
5. Adequate oral hygiene ((Full mouth plaque index (O'Leary, et al. 1972) <25%) at baseline
6. Adequate control of inflammation ((full mouth bleeding on probing (Ainamo and Bay 1975)) ≤25% at baseline

5.2 Exclusion Criteria

If any of the following criteria are met, the subject must be excluded from the study:

1. Systemic disease that would interfere with bone or wound healing and dental implant therapy (e.g. uncontrolled diabetes)
2. Systemic disease that would interfere with bone or wound healing and dental implant therapy (e.g. uncontrolled diabetes)
3. Any contraindications for general bone grafting and oral surgical procedures
4. Any anomalies of the sinus that could interfere with planned procedures
5. History of local irradiation therapy
6. Local inflammation, including untreated periodontitis
7. Medical conditions requiring chronic high dose steroid therapy

8. Treatment with an investigational drug or device within a 30 day period immediately prior to surgery at visit 2, or expected participation in any other investigational drug or device study during the conduct of this trial.
9. Antibiotic treatment or anti-inflammatory treatment within 4 weeks prior to surgery
10. History of alcoholism or drug abuse
11. Immunocompromised subjects
12. Subjects who smoke >10 cigarettes per day or tobacco equivalents or chew tobacco
13. Conditions or circumstances, in the opinion of the investigator, which would prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance or unreliability
14. Physical or mental disabilities that would interfere with the ability to perform adequate oral hygiene
15. Current pregnancy (pregnancy test) and breastfeeding women

5.3 Secondary exclusion criteria at sinus floor elevation

If the following criteria is met at sinus floor elevation, the subject must be excluded from the study:

1. Defects of the Schneider Membrane

5.4 Treatment Groups

In total 50 subjects will be randomize equally into test or control group (25 patients in each group).

The subjects in the test group receive sinus floor elevation with HA/TCP 10:90 (*Straumann® VivOss™*) via a lateral approach. In the comparator group, subjects receive sinus floor elevation with demineralized bovine mineral (Bio-Oss®) via a lateral approach.

Both groups follow the same schedule of assessments.

6 Investigational Device(s)

6.1 General Description of the Investigational Devices

All investigational devices used in this study are CE marked.

Straumann® VivOss™Straumann® VivOss™, is a synthetic bone graft substitute in granulated form. It consists of > 90% TCP (Tri-Calcium-Phosphate –$Ca_3(PO_4)_2$) and < 10% Hydroxyapatite ($Ca_{10}(PO_4)_6$ $(OH)_2$). The granules have a size of 250-1000 µm.

Straumann® VivOss™ is both osteoconductive and has a porous trabecular structure that resembles the interconnected porosity of human cancellous bone. Straumann® VivOss™ induces and guides the three dimensional regeneration of bone in the defect site into which it is implanted. It's intended to be used for applications in oral and maxillofacial surgery and dentistry for filling or reconstruction of multiple walled (artificial or degenerative) bone defects.

The Sponsor supplies the product. It shall be used according to the instructions of the manufacturer.

6.1.1 Instruction for Use, Handling, and Labelling

For the instructions for use, handling and labelling, the investigator has to refer to the instruction for use of the study products. In case of any questions, comments or doubts, the investigator can contact Institut Straumann AG.

In the event of a problem with the study product the monitor or the study manager should be informed immediately. In case of missing or lost study products all discrepancies have to be documented.

6.1.2 Storage

The study products provided by the Sponsor are to be used for the subjects enrolled in the clinical study only. The study products should be stored in its original container until used and as it is indicated in the package insert.

Handling of unused study products can be found under section 6.3 Device Accountability.

6.1.3 Risks and Benefits of the Investigational Device and Clinical Investigation

The investigational and control devices used in this study are CE marked. The clinical procedures performed are standard procedures.

The risk analyses for the investigational devices were conducted according to ISO 14971.

It can be stated that the risk from the investigational devices is low and acceptable, and the identified risk hazards from the devices are justified when considered against the significant clinical benefits provided. The investigational devices raise no new questions for safety and effectiveness as compared to similar devices. The investigator follows the instructions for use recommended by the manufacturer.

The possible risks and discomforts that may be associated with participation in this study are no different than having the same procedure (Sinus floor augmentation and placement of dental implants in a 2 stage approach) done without participation in this study. The following risks and adverse events can occur:

- General risks that exist with surgical procedures in the oral cavity: Bleeding and bruising, pain and swelling after the surgical procedure. Infections in the soft and hard tissue, delayed healing, recession of the gum and/or bone, temporary or permanent nerve damage in the jaw, oro-sinus or oro-nasal fistulas and possible rejection are very rare.
- General risks that exist with a surgical procedure using barrier membranes and can therefore not be completely ruled out: soft tissue dehiscence (tissue damage), haematoma, pain, increased sensitivity and redness due to inflammation
- Gingival inflammation (oral hygiene dependent): Oral hygiene instructions are given and oral hygiene procedures performed to prevent gingival inflammation.
- The following are examples of complications that can generally occur with a surgical procedure in the oral cavity and can therefore not be completely ruled out:
  - Slight pain and tenderness the first days after surgery
  - Slight swelling and redness the first days after surgery
- Pregnancy during the study, in particular at surgery, and the use of x-rays / CBCTs during pregnancy constitutes an additional risk to the foetus. Therefore neither

pregnant women nor women who plan to become pregnant must take part in this study.

The bone biopsy will be retrieved following a minimally invasive procedure during conventional dental implant bed preparation. The bone biopsy is retrieved by means of a trephine burr with a inner diameter of 2.8 mm during implant bed preparation. The dental implant bed preparation is finalized and the dental implant placed according to the protocol.

Dental implants can improve the bite and chewing ability, as well as the aesthetics and the feeling to have natural teeth. In addition, the subject can profit from an intensive and regular dental care as participant.

6.2 Comparators

All comparators used in this study are CE marked. The Sponsor supplies the products.

Geistlich Bio-Oss®

The control device is *Geistlich Bio-Oss*® spongiosa granules (Geistlich Pharma AG, Wolhusen, Switzerland), 0.25-1 mm in diameter. It's a natural bone mineral of bovine origin. It shall be used according to the instructions of the manufacturer.

6.3 Additionall products used in the study

Geistlich Bio-Gide®

Geistlich Bio-Gide® is a pure collagen matrix. The collagen is extracted from veterinary certified pigs and is carefully purified. It shall be used according to the instructions of the manufacturer.

6.4 Device Accountability

The investigator has to confirm the receipt of the study products and ensures secure and proper storage. After treatment of the last subject, remaining study products that have not been used in the study should be returned to the Sponsor or destroyed on site according to the sites standard procedures. The investigator should maintain accountability records of all study products received, used, and returned during the course of the study.

6.5 Device Complaints

Defects in the investigational devices should be reported to the Sponsor by the investigator immediately upon discovery.

Defects in the comparators should be reported by the investigator to the manufacturer of the comparators.

7 Study Procedures

7.1 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The investigator will also explain to each subject

any alternative procedures. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason and that they will be offered an alternative treatment related to their dental condition. Subjects will be advised of the need for the prescribed follow-up visits for their ongoing care and well-being and for the collection of relevant study data. All subjects must be willing to return to the clinical centre to complete such visits. The written informed consent has to be obtained from all subjects before any study related procedures are performed. This Institutional Review Board (IRB)/ Ethics Committee (IEC) approved consent form must be signed and dated by the subject and the investigator. If the investigator intend to start with any study related procedure on the same day the subject signed the informed consent, the investigator and the subject have to indicate the exact time of the informed consent on the informed consent form.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed on the new information, given a copy of the revised form and give their consent to continue in the study.

Investigators should keep one original signed informed consent document in the investigators file or the CRF folder and hand out a second signed informed consent document to the subject.

7.2 Pregnancy Test

Women of childbearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) must perform a pregnancy test (urine based) during screening. The test result must be documented in the source data.

During the study it is recommended to use highly effective contraceptive method (failure rate less than 1% per year) such as injectable, combined oral contraceptives or hormonal intrauterine devices (IUDs).

7.3 Demographics

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

7.4 Medical History & Dental History

The dental history & medical history has to be obtained at the screening visit. It should include dental status information including extraction socket position according to FDI and description of opposing and adjacent dentition.

Oral hygiene assessment could be performed according to the standard of care at the site (although it is not mandatory, it is recommended to use the Full Mouth Plaque Index (PI) according to O'Leary et al. 1972[22] and the Full Mouth Bleeding on Probing (BoP) Index according to Ainamo and Bay 1975.[23]).

Full mouth PI (O'Leary et al. 1972) should be measured on each single tooth mesial, distal, facial and lingual with the following formula:

$$\text{Percentage of total surfaces with plaque} = \frac{\text{No. of surfaces with plaque} \times 100}{\text{Total no. of surfaces}}$$

Full mouth BoP (Ainamo and Bay 1975) should be measured on each single tooth mesial, distal, facial and lingual with the following formula:

$$\text{Percentage of total surfaces bleeding} = \frac{\text{No. of surfaces bleeding x 100}}{\text{Total no. of surfaces}}$$

Current diseases will be evaluated by the investigator based on the information available (letter from general physician or oral communication with the subject).

7.5 Inclusion / Exclusion Criteria

See 5.1. and 5.2

7.6 Cone Beam CT

In order to perform radiographic measurements of the residual bone height a cone beam computed topography (CBCT) not older than 12 months should be available. Dental cone beam CT scan (CBCT) technique provides a 3-dimensional view of the area of interest and therefore offers sufficient information on sinus anatomy to plan for sinus floor elevation.

7.7 Adverse Events (please see section *9. Definitions of Adverse Events and Device deficiencies (from ISO 14155)*)

Any adverse event must be documented at each study visit until the end of the study.

7.8 Concomitant Medications

Any concomitant medication as well as changes in the concomitant medication, procedures, or supportive therapies must be documented at each study visit (except vist 1) until the end of the study.

7.9 Randomization

Subjects will be randomized either to the test group receiving Straumann® VivOss™ or comparator group receiving Geistlich Bio-Oss®. The master randomization list will be kept in a secure repository in the office of the Sponsor.The study centers have to contact the Sponsor by email or phone to request randomization of a subject, the Sponsor will send a randomization form including randomization details via email or fax. Although this study is not blinded, no access to the randomization list will be available to the study centre, the external Monitors, the subjects and the Straumann non-Clinical-Research project team.

Site/s of Biopsy

The site of biopsy in each sinus depends on the number of implants to be placed in the sinus. If more than one implant will be placed the most preferred site will be position 6, followed by position 5, followed by position 7, the least preferred position is position 4.

If more than one implant is placed, the investigator should take 2 biopsies following the preference list above. The second biopsy should be taken as backup in case the first biopsy cannot be evaluated.

Bilateral Sinus Floor Augmentation

If a patient needs augmentation in both sinus, one sinus is randomised as study sinus. If the sinus is randomized into test group and receives Straumann® VivOss™, the opposite sinus should be augmented with Geistlich Bio-Oss® and vice versa. In bilateral patients biopsies should be taken from both sinus according to the instructions above.

7.10 Augmentation

The Sponsor recommends to follow the lateral window technique as described in the ITI Treatment Guide Volume 5 (2011). A collagen membrane *Geistlich Bio-Oss*® should be used to stabilize the bone window, this membrane should cover the complete window and should not consist of several pieces. Afterwards the gingiva should close the wound completely and should be sutured without any tension.

7.11 Secondary Inclusion criteria

See 5.3.

7.12 Intra-oral Photographs

Digital intra-oral photographs in raw-format should be taken at each study visit to document the procedures:

Visit 2: At surgery visit the investigator should take the following lateral pictures:
- before surgery
- before removing the window
- open sinus
- filled sinus
- window back in place
- membrane placed on window
- after suture

Visit 3: Lateral pictures:
- wound before suture removal
- wound after suture removal

Visit 4: vertical pictures:
- open flap
- after biopsy
- before implant placement
- implant placed flap open
- after suture

Visit 5: vertical pictures
- wound before suture removal
- wound after suture removal

Visit 6: vertical pictures
- before loading
- after loading

Photographs should be labelled as below for easy identification of the subject:

Study CR 03/13: 0313
Visit number: _V1
Patient No.: _01 25

e.g. 0313_V1_0125
0313_V3_0205

7.13 Suture removal

Sutures should be removed according to the standard of care at the clinic.

7.14 Biopsy

The bone biopsies are retrieved in both the test and the comparator group.

The bone biopsies will be retrieved from the central part of the dental implant osteotomy and will be processed together with the trephine burr. The biopsies will be immersed and fixed in buffered formalin. Further processing of the biopsy and evaluation of the histologies is described in detail in a separate technical procedure protocol. The biopsy-samples will be labelled with:

- Patient number
- Position (FDI)

7.15 All biopsy-samples will be analysed centrally in Zürich, Switzerland. Implant placement

After the biopsy the study center should follow their standard of care regarding implant bed preparation and implant placement. The details of the used implant have to be documented.

7.16 Wound healing assessment

Wound healing details have to be documented.

7.17 Periapical x-rays

A periapical x-ray has to be taken to document the success of the implant in regards to radiolucency.

7.18 Implant survival

Implant survival has to be documented

7.19 Implant success

An implant will be deemed a success if all of the following success criteria (according to Buser et al 1992[24]) apply:

- Absence of persisting subjective discomfort such as pain, foreign body perception and or dysaesthesia (painful sensation)
- Absence of a recurrent peri-implant infection with suppuration (where an infection is termed recurrent if it is observed at two or more follow-up visits after treatment with systemic antibiotics)
- Absence of implant mobility on manual palpation

- Absence of any continuous peri-implant radiolucency

8 Study conduct

8.1 Visit Windows

The goal should always be to keep the given time point of each visit. However the time windows given below are the limits to be kept to perform according to the protocol.

Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Informed Consent	**Screening Visit**	**Sinus elevation (Baseline)**	**Wound healing assessment**	**Implant placement**	**Wound healing assessment**	**Initial implant loading**
28-2 days before screening	**14-0 days before Baseline**	**Day 0**	**Day 7-14**	**6 months ± 7 days**	**2 weeks after visit 4**	**4 months ± 1 month after visit 4**

8.2 Screening Failures

Any subject that has signed the informed consent form, is not randomized and does not receive the study device is considered a screening failure. In the event of a screening failure, the case report forms should be completed up to the visit when the subject was determined to be a screening failure. The “study termination form” should also be completed and a new subject should be recruited if the recruitment period is ongoing.

In case of a screening failure according to an eligibility criterion that may be re-evaluated at a later time point (e.g. oral hygiene), a re-screening of the patient is possible as judged by the investigator if the recruitment period is ongoing. In this case, a “re-screening form” should be completed instead of the “study termination form”.

8.3 Subject Completion / Withdrawal

It is possible that a 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 relevant study data. All subjects must agree to return to the clinic to complete these follow-up visits.

The investigator may withdraw any subject from the study in the case of:

- non-compliance with the protocol
- a serious adverse event or an adverse event, in the opinion of the investigator, which prevents the subject’s further participation in the study.

If a subject is withdrawn from the study as outlined above, the subject must be followed for reporting of adverse events. Withdrawn subjects will be followed according to the standard of care at the study centre.

8.4 Subject Replacement Policy

For any subject who for any reason drops out of the per-protocol population a new subject with a new number should be allocated if the recruitment period is ongoing.

8.5 Missed Visits

In the event a subject misses a visit, the subject should be recalled as soon as possible. At a minimum, the subject should be contacted twice to reschedule. If the subject is not reached by telephone, a certified letter should be sent to the subject. The study monitor should be contacted to discuss options for the subject's continuation in the study. If all attempts to contact the subject have failed, the subject should be considered lost to follow-up and the "Study Termination Form" should be completed.

8.6 Protocol Deviations

Deviations from the procedures established in the protocol are not permitted. If a deviation occurs, the study monitor must be contacted immediately. The deviation must be documented and investigated. A written statement from the investigator on whether the deviation will affect the integrity of the study will be required.

Any deviation from the protocol (including deviations of the visit dates) may jeopardise the study outcome. Non-compliance of the subjects as well as of the investigators may lead to the closure of the respective centre.

9 Definitions of Adverse Events and Device Deficiencies (from ISO 14155)

9.1 Investigational medical device

Medical device being assessed for safety or performance in a clinical investigation
NOTE: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

9.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
NOTE 1: This includes events related to the investigational device or the comparator.
NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).
NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

9.3 Expected adverse events

The following adverse events (irrespective of relatedness) can be expected:

- General risks that exist with dental surgical procedures: Bleeding and bruising, pain and swelling after the surgical procedure. Infections in the soft and hard tissue, delayed healing, recession of the gum and/or bone, temporary or permanent nerve damage in the jaw, oro-sinus or oro-nasal fistulas and possible rejection are very rare.
- The following are examples of complications that can generally occur with a surgical procedure using implants and can therefore not be completely ruled out:
    - Slight pain and tenderness the first days after surgery

    - Slight swelling and redness the first days after surgery
- Gingival inflammation (oral hygiene dependent): Oral hygiene instructions are given and oral hygiene procedures performed to prevent gingival inflammation. The occurrence of gingival inflammation will be monitored by means of the modified gingival index and if it occurs the investigator will provide treatment as needed and repeat oral hygiene instructions.
- General risks that exist with a surgical procedure using barrier membranes and can therefore not be completely ruled out: soft tissue dehiscence (tissue damage), haematoma, pain, increased sensitivity and redness due to inflammation.

In regard to wound healing assessments only clinically significant symptoms that are outside the normally accepted range (as judged by the clinician) will be reported as adverse events. This includes, but not restricts to:

- Excessive or progressively increasing pain or discomfort
- Excessive swelling
- Signs of infection (e.g. suppuration)
- Wound / soft tissue breakdown (e.g. soft tissue necrosis, flap dehiscence)
- Any other condition or observation deemed outside of the normal range of healing characteristics

9.4 Serious Adverse Event (SAE)

Adverse event that:
a) led to a death,
b) led to a serious deterioration in health that either:
1) resulted in a life-threatening illness or injury, or
2) resulted in a permanent impairment of a body structure or a body function, or
3) required in-patient hospitalization or prolongation of existing hospitalization, or
4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.
NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

9.5 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.
NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional misuse.

9.6 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

9.7 Unanticipated Serious Adverse Device Effect (USADE)

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.
NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

9.8 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

9.9 Assessment of Adverse Events

Each adverse event should be assessed according to the categorization charts for Adverse Events and Device deficiencies (from ISO 14155).

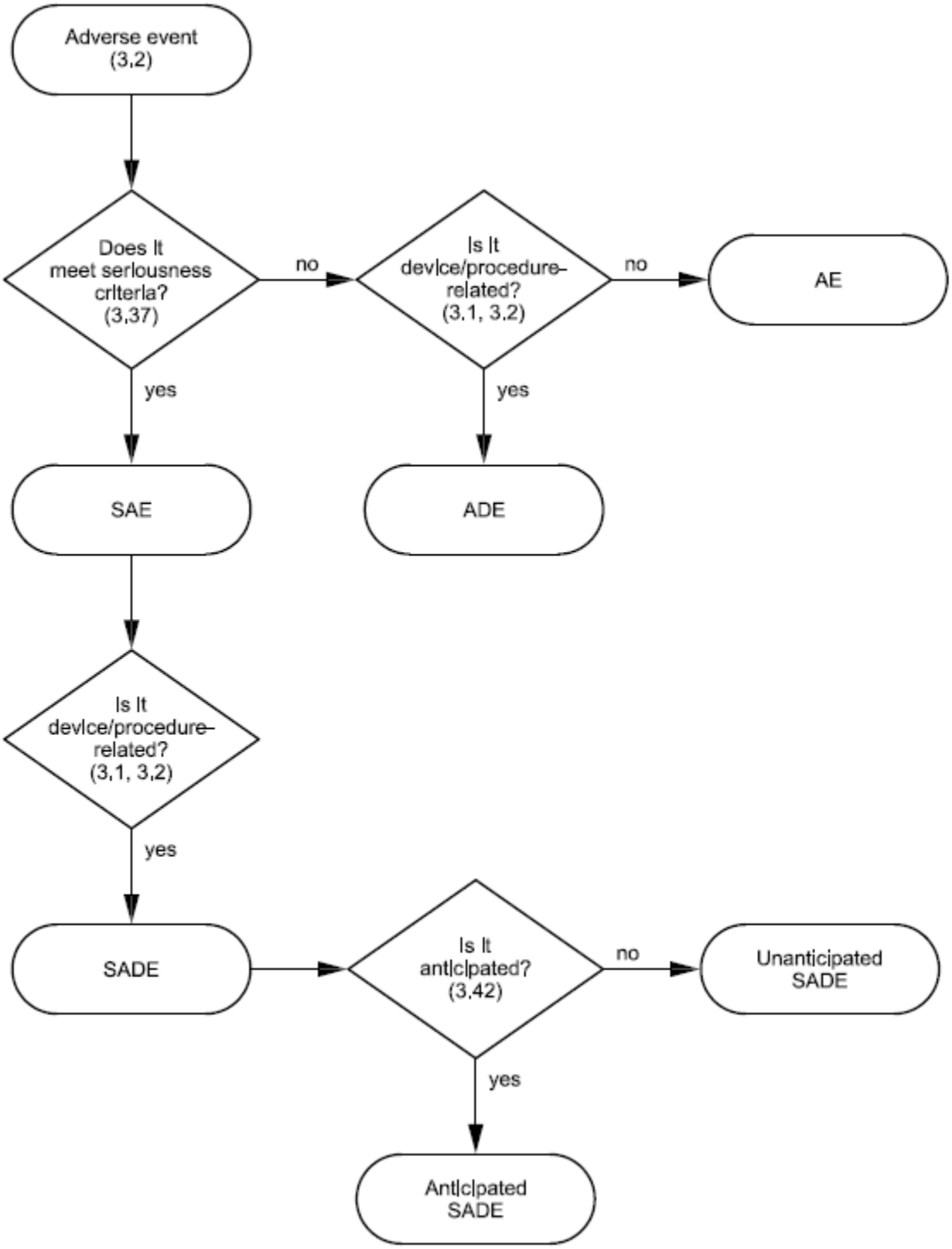

Figure 2: Adverse event categorization chart (from ISO 14155)

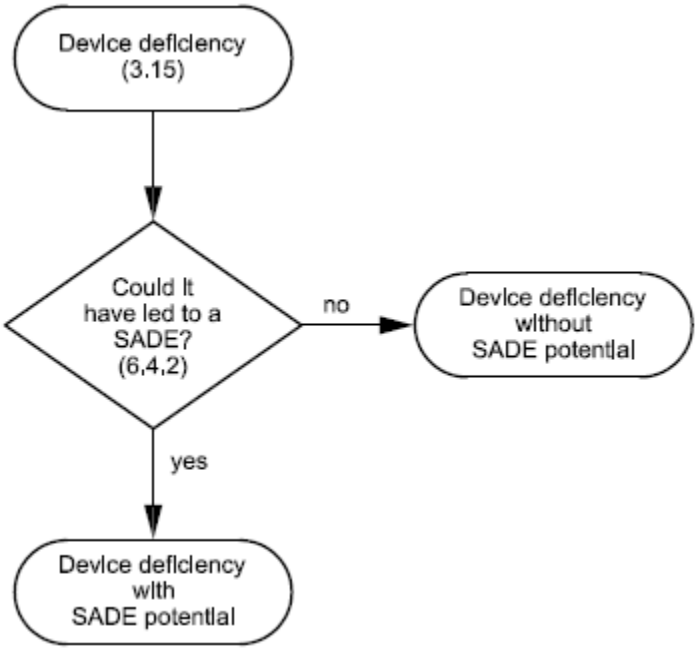

Figure 3: Device deficiency categorization chart (from ISO 14155)

9.10 Severity of Adverse Events

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

- Mild – discomfort noticed, but no disruption in daily activities
- Moderate – discomfort sufficient enough to reduce or affect normal daily activity
- Severe – Inability to work or perform normal daily activity

9.11 AE Reporting

In case of an occurrence of an AE an AE Form in the CRF must be filled out within reasonable time. Occurred AEs must be addressed at the next monitoring visit. An annual safety report should be created and send to the EC by the Sponsor.

9.12 SAE Reporting

If an SAE bears an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other it has to be reported immediately (max. 2 days).

Any other reportable event related to the medical device under investigation or due to study related procedures must be reported within 7 days.

All SAEs must be reported via the SAE reporting form (which will be provided by the Sponsor) according to MEDDEV 2.7/3 (Dec. 2010).

The investigator should notify the Sponsor within 24 hours of first learning of the serious adverse event.

Contact address:

Clinical Research, Institut Straumann AG
Phone: 0041 61 965 11 11
Fax: 0041 61 965 11 10

The monitor may be required to collect further information for a final evaluation of the event. While the Sponsor is responsible for interactions with Health Authorities and Ethics Committees, it is the duty of the local investigator to keep the Sponsor informed.

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. Close contact to the subjects should help to get relevant information in a timely manner. The investigator should report any SAE as soon as he has knowledge of the event within the above time frame irrespective of when the actual event occurred.

9.13 Monitoring / Follow-up of Subjects with Adverse Events

Any AE that occurs in the course of this study must be monitored and followed up 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

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

9.14 Pregnancy

If a female subject becomes pregnant during the course of the study, the study visits should be completed as scheduled. Any study assessments that could potentially interfere with the pregnancy should be avoided until after the pregnancy (e.g. CBCTs, radiographs, etc.). The pregnancy should be recorded as an adverse event, whereas the start of pregnancy will be recorded as the start date of the AE and the date of child birth will be recorded as the end date.

10 Statistical Procedures

The statistical analysis principles described below will be supplemented by a detailed statistical analysis plan (SAP) which will be written after the first patients have performed visit 2 and will be finalized, based on the findings of the data review meeting, before the database is locked.

10.1 Statistical Analysis

The statistical analysis will be performed by an external partner.

Descriptive summary statistics will be computed for all parameters documented on the case report form (CRF). Quantitative parameters will be described by seven-point scales with mean, standard deviation, median, quartiles, minimum and maximum. For qualitative

variables absolute and relative frequencies will be given. All descriptions will be done separately for treatment groups and visits.

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

10.2 Statistical Hypotheses

The primary endpoint of this study is the histological evaluation of the ratio of newly formed bone to residual bone graft in *Straumann® VivOss™* compared to *Geistlich Bio-Oss®* at visit 4 (6 month ± 7 days, after sinus elevation).

In this study the following hypothesis will be tested

Straumann® VivOss™ combined with Bio-Gide shows a significantly higher ratio of newly formed bone to residual bone graft compared to *Geistlich Bio-Oss®* combined with GeistlichBio-Gide at visit 4 (6 month ± 7 days, after sinus elevation).

- T: Test Group
- C: Comparator Group

Testing for Superiority (based on the per protocol (PP) data set):

H_{0S}: $T = C$

H_{1S}: $T \neq C$

H_{0S} is the null hypothesis, claiming that there is no difference in the true mean of ratio of newly formed bone to residual bone graft after 6 months between the test group and the negative control group

H_{1S} is the alternative hypothesis claiming that the true mean change of ratio of newly formed bone to residual bone graft after 6 months is unequal in the two treatment groups; either higher or lower in the test group than in the negative control group.

T is the true mean at 6 months of the ratio of newly formed bone to residual bone graft in the test group.

C is the true mean at 6 months of the ratio of newly formed bone to residual bone graft in the control group.

The secondary efficacy variables in this clinical study are:

- Survival rate of study implants evaluated at visit 6 (initial implant loading)
- Success rate of study implants evaluated at visit 6 (initial implant loading)

10.3 Sample Size Calculation

Sample size calculations were performed for a clinical relevant difference between test and comparator across a given range of standard deviations, and with the two-sided unpaired t-test under a significance level α =5% and with a power β = 80%.

a) Sample Size for Test to Show Superiority of Test Group vs. Control Group

Based on a recent pre-clinical study a difference of the means of the ratio of newly formed bone to residual bone graft of approximately 0.4 can be expected in favour of the test treatment compared to the control. Considering a common standard deviation of 0.5, 25 subjects per group would be necessary to confirm this clinically relevant difference statistically.

Table 1: Sample size for superiority based on Δ = 0.4:

Common SD [mm]	**0.425**	**0.45**	**0.475**	**0.5**	**0.525**	**0.55**	**0.575**
n Test	18	20	23	25	28	30	33
n Control	18	20	23	25	28	30	33

10.4 Populations for Analysis

10.4.1 Per Protocol Set (PP)

Randomized subjects who terminated the study and in whom no major protocol violations have been observed.

10.4.2 Full Analysis Set (FA)

This data set will include all randomized subjects who have received at least one study device and from whom at least one measurement of post randomization data is available. It will include subjects even with major protocol violations and premature termination. The FA Set includes the PP Set.

10.4.3 Safety Analysis Set (SA)

This data set will include all subjects who have received at least one study device. The SA Set includes the FA Set.

10.4.4 Not Treated (NT)

Subjects enrolled in the study who did not receive the study device will be excluded from the analysis.

10.4.5 Final Analysis

An interim analysis will not be performed. The final analysis of all endpoints will be performed at the end of the study.

11 Data Management

11.1.1 Data Collection

Data should be recorded on the appropriate Case Report Form (CRF) for all study subjects from whom informed consent is obtained, and no study treatment should be administered without written informed consent. CRFs will be retrieved by the study monitor during the monitoring visits and subsequently sent to the data manager. Incoming data will be reviewed to identify inconsistent and/or missing data. Data problems will be addressed by written queries to the site.

11.1.2 Case Report Forms

Standardized CRFs will be provided by the Sponsor to the site. The investigator is responsible for completion of the CRFs in a timely manner and should be up to date with the documentation before each monitoring visit.

11.1.3 Data Entry and Management

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. The investigator will be queried on issues concerning completeness and consistency.

All above mentioned tasks will be carried out according to Straumann Standard Operating Procedures, except for those tasks performed by Straumann contracted Contract Research Organizations (CRO), where the CRO procedures shall be used.

12 Regulatory and Ethical Requirements

12.1 Basic requirements

The principal investigator/co-investigator shall confirm the eligibility of the subject by the screening test and confirm the conformity to the inclusion/exclusion criteria at the subject enrolment.

Also, the principal investigator/co-investigator shall keep knowledge about the subject's health condition by retaining the communication path to the subject for the emergency during the follow-up period, etc. Also, he/she shall make an effort to collect and transfer the safety information relevant to the investigational device with the cooperation of the relevant peoples involved to this study. In case of the occurrence of the adverse event, the principal investigator/co-investigator shall provide an appropriate treatment to ensure the subject's safety.

A Sponsor shall collect and examine information that is necessary for properly conducting a clinical trial, with respect to matters concerning the quality, efficacy, and safety of the investigational device and provide the head of the medical institution with such information.

Whenever the Sponsor finds any of the items such as disease, injury or death suspected due to adverse device effect, infection due to the investigational device or other events relates to the effectiveness or safety of the investigational device, Sponsor shall promptly notify the principal investigator and the head of the medical institution thereof.

12.2 Informed Consent

Each subject will be informed by the investigator of the overall requirements/procedures of the study after explaining the purposes of the study, the nature of the planned treatment and alternative procedures. In addition, he/ she will explain any risks, possible complications and benefits of the proposed treatment. The Institutional Review Board (IRB) approved consent form will be provided by the Sponsor.

The informed consent form will be valid only after it is dated and bears the name and signature of the principal investigator/co-investigator and subject.

The principal investigator/co-investigator shall provide the copy of it after it is dated and bears the name signature of the principal investigator/co-investigator and subject.

The informed consent document is written in accordance with the “Declaration of Helsinki” (as adopted by the 18th World Medical Assembly, 1964, and as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington (2002), Tokyo (2004) and Seoul (2008).

When the principal investigator/co-investigator obtained any information that might influence the subject's intent to participate in the clinical trial, the principal investigator/co-investigator shall promptly give such information to the subject, document the communication of the information, and confirm whether the subject is willing to continue his or her participation in the clinical trial.

The principal investigator, in such cases as stipulated under the preceding paragraph, shall revise the explanatory documents without delay whenever it is deemed necessary.

When the explanatory documents are revised pursuant to the preceding paragraph, the principal investigator shall report the fact to the head of the medical institution and obtain the subject's consent to continue his or her participation in the clinical trial.

12.3 Institutional Review Board / Ethics Committee

Prior to initiation of any study procedures, the protocol, sample of CRF, explanatory documents and informed consent form will be submitted to an IRB or Ethics Committee for review and approval from the viewpoint of ethical, scientific and medical appropriateness. In addition, any amendments to the protocol or informed consent must be reviewed and approved by the IRB or Ethics Committee. The Sponsor must receive a letter documenting the IRB / Ethics Committee approval at the clinical site prior to the initiation of the study.

The investigator is responsible for providing the appropriate reports to the IRB or Ethics Committee during the course of the clinical study.

12.4 Regulatory Compliance

This study will be performed in compliance with the Declaration of Helsinki, ISO 14155, this protocol and the relevant local regulations and laws.

13 Study Management

13.1 Reports and Record Management

13.1.1 Investigator Records

The investigator will receive an investigator file with all required study documents, including the instructions for use, protocol, CRF, informed consent, study contract and confidentiality agreement, insurance certificate, IRB/ IEC approval, CV of investigator and various other documents. Prior to the initiation of the study the investigator has to provide several documents including a signed confidentiality agreement, the curriculum vitae of the investigator(s), a signed copy of the final protocol and any amendments, a signed copy of the clinical study agreement with the Sponsor and various other documents on request.

13.1.2 Case Report Forms

The investigator shall supply the Sponsor on request with any required background data from the study documentation or any other clinical records. This is particularly important when errors in data transcription are suspected. The investigator will be responsible for the accuracy of the data entered in the case report form. All entries must be written in black or blue ink and all deletions, additions or changes must be initialled and dated (additional information sheet on how to fill out the CRF). The forms must be available for review/ collection to designated Straumann representatives at each scheduled monitoring visit. The investigator will also allow the Straumann representative and/ or regulatory bodies to review the data reported in the CRFs with the source documents as far as is permitted by local regulations and provided that the subject confidentiality is protected.

13.1.3 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. Certain data recorded in the CRF can be considered as source data. In this study the following data recorded in the CRF can be considered as source data: Full Mouth Plaque Index (PI) according to O'Leary et al. 1972 and the Full Mouth Bleeding on Probing (BoP) Index according to Ainamo and Bay 1975. All source documents pertaining to this study will be maintained by the investigator and made available for inspection by authorized persons and for source data verification during monitoring visits. 100% of source data verification will be performed on critical variables. Besides of general information the investigator has to document each and every requested data point of the CRF/protocol first in his source data. The transcription of these source data into the CRF might be done later by the investigator or authorized designee.

13.1.4 Records/data Retention

Originals of the radiographs, casts, or other items and originals of the study records and clinical data forms will be maintained by the study monitor in the file established for this study. All study documentation (CRFs, Investigators files, subject x-rays and photographs) should be kept at the study site after the study is completed for at least 15 years following the completion of the study as determined by the Sponsor. The investigator should be available to answer any queries associated with the study during this time. If the investigator is no longer working at the site, he is obliged to inform Straumann who will be in charge of the archived documents and who is responsible to answer questions once he is not at the site. If the documents are moved to another location the investigator must inform Institut Straumann AG about the move. 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 standard operating procedures.

13.1.5 Subject Data Protection

The name of the subject as well as all other personal data will be kept under the strict confidence by the investigator. If in case for medical reasons, it will be necessary during the course of the study to identify the subject this will be done under attention of the medical secrecy. The investigator will assure that all CRFs and other documents that will be handed out to Institute Straumann AG will not contain any personal subject data. The investigator will

prepare a separate list which will allow the identification of the subject. This list will contain subject numbers, initials, names and addresses of the subject and will be filed in the investigator's file.

During the regular monitoring visits, audits or inspections by the authorities, the subject cards will be inspected by authorised persons (e.g. monitors, auditors). These persons are committed legally on their secrecy.

13.2 Quality Control and Assurance

13.2.1 Monitoring (general aspects)

Straumann will assign a qualified individual to monitor the study. The general monitoring procedures for this study are described below. In general the monitor has to follow the applicable laws and guidelines during all monitoring activities.

The monitor will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study.

It is understood that the responsible Straumann monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial including the CRFs and other pertinent data, provided that the subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor will need to have access to storage locations of study devices and study supplies, to treatment/examination rooms and rooms where any study related activity takes place, and to all records associated with the study as well as to all other original patient records/source documents to verify the entries on the CRF. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problem detected in the course of these monitoring visits is resolved.

13.2.2 Pre-study Visit

The main purpose of the pre-study visit is to conduct a detailed discussion of the planned study, based on the draft protocol and eCRF/CRF (if available). If initially only a general outline exists and development of a study protocol largely depends on substantial input from the investigator, all relevant information has to be obtained in the pre-study phase to allow for the writing of the protocol and the designing of the eCRF/CRF.

13.2.3 Study Initiation Visit

If the required documentation including the insurance certificate, the devices and all study supplies as well as the IEC approval and the approval of the authorities (if applicable) are on file/on site, the monitor is allowed to perform the study initiation visit. The investigator(s), co-investigator(s) and all persons to whom the investigator has delegated significant study-related duties should be present for the initiation visit. The investigator(s), co-investigator(s) or any other persons to whom the investigator has delegated significant study-related duties are not allowed to perform any subject related action before the study initiation visit.

The monitor will address issues regarding the performance of the study with focus on the responsibilities of the investigator and co-workers during the initiation visit in detail with all persons involved, if not previously discussed and documented.

13.2.4 Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically.

- The protocol is being properly followed
- The IECs and authorities approved or has been notified of any protocol changes
- Informed consent has been obtained for each and every subject before any subject related activity
- Accurate, complete, and current records are being maintained, and the information recorded on the CRFs is representative of the subject's record and other source data (source document verification)
- Accurate, complete, and timely adverse event and serious adverse event reporting is followed
- The reason for a subject's withdrawal has been documented
- Reports are being submitted to the IEC, authorities and to the Sponsor
- The appropriate staff is carrying out the study activities
- All logs are valid and up-to-date
- Study devices and study supplies are stored and accounted correctly
- etc.

The investigator must provide to the Sponsor and/or representative the necessary study records for a thorough review of the study's progress.

At monitoring visits radiographs, CRFs, photographs, casts and other study documents might be collected.

13.2.5 Close out Visit

All routine monitoring functions must be completed prior to the study termination visit. During this last scheduled visit the monitor will also focus on the responsibilities of the investigator after the study is closed. The site should have answered any open query before the monitor schedules this visit, and the database (if not already closed) should be cleaned and locked. The monitor has to follow-up the finalization of all study logs and has to prepare copies of all documents necessary for the TMF as well as final check the IF for completeness. The monitor should prepare the IF and CRF in a matter that allows the investigator easy archiving.

13.2.6 Study Termination

The study can be discontinued early at the discretion of the principle investigator or the Sponsor in the case of any of the following:

- Occurrence of AEs unknown at the start of the study in with respect to their nature, severity, and duration, or the unexpected excessive incidence of known AEs
- New scientific knowledge obtained after the start of the study showing the ethical claim of the study is no longer valid

If the study or a study site is terminated before the aspired end of the study for any reason, the investigator should contact all active study subjects. Afterwards the investigator should apply the standard of care for implant therapy.

If the study is temporarily interrupted for any reason the subjects should be treated at the discretion of the investigator. Each investigator should take care that none of his subjects exceeds the absolute treatment time, unless it is medically indicated.

In terminating or temporarily interrupting situations, Straumann and the investigator will assure the adequate consideration is given to the protection of the subject's interests.

13.2.7 Centre discontinuation

The study centre might be closed and the study terminated under the following circumstances:

- The centre is not recruiting a sufficient number of subjects or is unlikely to recruit a sufficient number of subjects
- The centre does not respond to study management requests
- Repeated protocol violations have been discovered

13.2.8 Audits and Inspections

The study may be audited at any time by Institute Straumann AG or inspected by the regulatory authorities. The investigator and his team will make themselves available when the auditors or the inspectors are present, giving them access to the site, the study material, and to subject files. The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Straumann or its designees or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

The subjects' confidentiality must be safeguarded and data checked during the audit should remain confidential.

13.3 Protocol Amendments

Once the first subject has entered the study, 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.

If changes to the protocol are proposed, they shall be discussed with the study manager in a timely manner. IEC approval and Authority approval is required for any change in the protocol or in the informed consent that may affect the scientific soundness of the study or the right, safety, or welfare of the. The change in the protocol can not be implemented until the approvals are obtained. Once the investigator and the Sponsor have accepted the changes, a written amendment to the protocol will be sent the investigator for signature.

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.

13.4 Publications

The study results are planned to be published. All study results and any new invention or discovery and the rights deriving there from shall be owned solely and exclusively by Straumann. Analysis of data will be done by Straumann and the final manuscript being prepared in conjunction with Institut Straumann AG. Straumann reserves the right to comment upon any additional manuscripts intended for publication or public presentation which encompass information obtained during clinical studies sponsored or supported by the company. Investigator(s) will be requested to submit their final manuscript to Straumann and will receive comments from the company within a maximum period of 45 days.

14 AGREEMEEMENT SIGNATURES

Protocol: CR 03/13

Title: A randomized controlled clinical trial to investigate the capability of *Straumann*® *VivOss*™ compared to *Geistlich Bio-Oss*® in sinus floor augmentation

Date: 19 January 2015

Version: 6.0

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

Signatures:

Name of Investigator	Signature of Investigator	Date (dd/mm/yyyy)

15 Appendix

Appendix 1: WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

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 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

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 not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. 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."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. 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 current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

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

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should 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.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

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

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

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

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

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, 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.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent 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.

29. 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 population. In such circumstances the physician should 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 should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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.

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

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the

object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

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