# Immediate Placement of the Straumann® Bone Level Tapered Implant with Early Loading in Single Tooth Gaps in the Maxilla and Mandible Compared to Delayed Placement

## CR 01/14

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**Version 5.0**

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## Abbreviations

| | |
|---|---|
| Ø | Diameter |
| ADA | American Dental Association |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ASADE | Anticipated Serious Adverse Device Effect |
| BLT | Bone Level Tapered |
| CBCT | Cone Beam Computed Tomography |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| DD | Device Deficiencies |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| FDA | Food and Drug Administration |
| GBR | Guided Bone Regeneration |
| GCP | Good Clinical Practice |
| GTR | Guided Tissue Regeneration |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| ISQ | Implant Stability Quotient |

| | |
|---|---|
| ITT | Intention To Treat population |
| mITT | Modified Intention to Treat |
| mm | Millimeter |
| mSBI | modified Sulcus Bleeding Index |
| Ncm | Newton centimeter |
| PP | Per Protocol population |
| PPD | Probing Pocket Depth |
| PSP | Photostimulable Phosphor |
| RFA | Resonance Frequency Analysis |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAF | Safety Population |
| USADE | Unanticipated Serious Adverse Device Effect |
| VAS | Visual Analog Scale |

## Synopsis

| | |
|---|---|
| **Study Title:** | Immediate Placement of the Straumann® Bone Level Tapered Implant with Early Loading in Single Tooth Gaps in the Maxilla and Mandible Compared to Delayed Placement as Control |
| **Study Protocol Number:** | CR 01/14 |
| **Study Registration:** | This protocol will be registered at clinicaltrials.gov before enrollment begins. |
| **Objectives:** | The aim of this randomized, controlled, multi-center study is to assess the clinical and radiographic outcomes of using a Straumann® Bone Level Tapered implant for immediate implantation following extraction of a tooth in the pre-molar and anterior region of the maxilla and mandible (test) compared to the outcomes of placing this implant in healed sites (control).<br>The **primary objective** is to demonstrate that the change in mean peri-implant marginal bone level changes (mesial and distal) from loading to 12 months post-loading of the test treatment will be no worse than the control treatments.<br>The **secondary objectives** of the study are to assess differences in clinical and radiographic outcomes between the test and control treatments at 12 months post-loading by looking at implant success and survival, buccal bone dimensional changes, implant stability, soft tissue changes, subject satisfaction, and adverse events.<br>An **additional objective** is to assess long-term differences in clinical and radiographic outcomes, as measured in the primary and secondary objectives, over the span of five years. |
| **Study Design:** | Post-market, prospective, randomized, controlled, multi-center study |
| **Subject Population:** | Male or female subjects 18 years of age or older who are in need of a single tooth extraction in the pre-molar or anterior region of the mouth and replacement with a dental implant; and meet all of the inclusion/exclusion criteria listed below. |
| **Inclusion Criteria:** | • Subjects must have voluntarily signed the informed consent form before any study related procedures<br>• Subjects must be males or females who are a minimum of 18 years of age<br>• Subjects who are in need of a single tooth extraction in the pre-molar or anterior region of the maxilla or mandible (ADA tooth positions 4-13 and 20-29) and replacement with a dental implant.<br>• Implants must be placed either immediately in an extraction socket or placed in a healed site (greater than 4 months healing) which has not been previously grafted.<br>• Planned site for implant must have a natural tooth both mesially and distally in the adjacent tooth positions<br>• Subjects must have opposing dentition (natural teeth, fixed or removable restorations)<br>• There must be sufficient bone at the implant site to achieve primary stability<br>• Subjects must be committed to the study and the required follow-up visits |

<table>
<tr><td></td><td colspan="3">• Subjects must be in good general health as assessed by the Investigator</td></tr>
<tr><td>Exclusion Criteria:</td><td colspan="3">• Subjects with a systemic disease that would preclude dental implant surgery<br>• Subjects with any contraindications for oral surgical procedures<br>• Subjects with mucosal diseases (e.g., erosive lichen planus) in the localized area around the study implant site<br>• Subjects with a history of local irradiation therapy in the head/neck area<br>• Subjects with any untreated endodontic lesions or untreated periodontal disease adjacent to the implant site<br>• Subjects receiving, or having a history of receiving, intravenous or subcutaneous antiresorptive agents, such as bisphosphonates<br>• Subjects with severe bruxing, parafunctional habits, or temporomandibular joint dysfunction<br>• Any implant sites where there will be a buccal dehiscence greater than 3 mm or there will be a fenestration of the implant<br>• Subjects with inadequate oral hygiene or who are unmotivated for adequate home care<br>• Subjects who have physical or mental handicaps that would interfere with the ability to perform adequate oral hygiene<br>• Subjects who are pregnant or intending to become pregnant during the duration of the study<br>• Subjects who are heavy smokers (defined as >10 cigarettes per day or >1 cigar per day) or chew tobacco<br>• Subjects who abuse alcohol or drugs<br>• Subjects who have undergone administration of any investigational device within 30 days of enrollment in the study<br>• 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, such as history of non-compliance or unreliability</td></tr>
<tr><td rowspan="8">Treatment Plan:</td><td>Visit #</td><td>Visit</td><td>Schedule</td></tr>
<tr><td>Visit 1</td><td>Screening</td><td>< 45 days from tooth extraction</td></tr>
<tr><td>Visit 2a</td><td>Tooth Extraction and Randomization</td><td></td></tr>
<tr><td>Visit 2b</td><td>Implant Surgery</td><td>Immediately at tooth extraction OR<br>17 weeks after tooth extraction</td></tr>
<tr><td>Visit 3</td><td>Immediate Post-Operative</td><td>10 days after implant placement</td></tr>
<tr><td>Visit 4</td><td>Uncover Implant (impression/index for provisional)</td><td>10 weeks ± 3 weeks after implant placement</td></tr>
<tr><td>Visit 5</td><td>Implant Loading</td><td>10 weeks ± 3 weeks post implant placement</td></tr>
<tr><td>Visit 6</td><td>Impression (for final restoration)</td><td>5 weeks post-loading</td></tr>
</table>

| | | | |
|---|---|---|---|
| | Visit 7 | Final Restoration | 10 weeks post-loading |
| | Visit 8 | 6-month follow-up | 6 months post-loading |
| | Visit 9 | Primary Endpoint | 12 months post-loading |
| | Visit 10 | Additional follow-up | 24 months post-loading |
| | Visit 11 | Additional follow-up | 36 months post-loading |
| | Visit 12 | Additional follow-up | 48 months post-loading |
| | Visit 13 | Additional follow-up | 60 months post-loading |
| **Study Products:** | Straumann® Bone Level Tapered implants with the SLActive® surface and Roxolid material, endosteal diameter 3.3 mm, 4.1 mm, and 4.8 mm, available in lengths of 8, 10, 12, 14 and 16 mm. | | |
| **Registration Status:** | Straumann® Bone Level Tapered implants with the SLActive® surface are CE marked products and are subject of cleared 510(k) pre-market notifications K140878 and will be used within the cleared indications. | | |
| **Primary Analysis:** | The primary analysis will be conducted after all subjects complete the 12 months post-loading visit. Baseline is implant loading. | | |
| **Primary Parameters:** | • Mean crestal bone level change | | |
| **Secondary Parameters** | • Implant success and survival<br>• Dimensional changes of the buccal bone measured on cone beam computed tomography images<br>• Implant stability as measured by resonance frequency analysis (implant placement, implant loading, and final restoration)<br>• Changes in soft tissue (gingival and papilla margins – baseline at final restoration)<br>• Subject satisfaction (esthetics, function, and level of pain)<br>• Adverse events and adverse device effects incidence | | |
| **Additional Analysis:** | Additional analysis will be done at 24, 36, 48, and 60 months post-loading | | |
| **Additional Analysis Parameters:** | • Mean crestal bone level changes<br>• Implant success and survival<br>• Buccal bone dimensional changes measured on CBCT images<br>• Changes in soft tissue (gingival and papilla margins)<br>• Subject satisfaction (esthetics, function, and level of pain)<br>• Adverse events and adverse device effects incidence | | |
| **Statistical Considerations** | The hypothesis is the mean change in crestal bone from implant loading to 12 months post-loading for the test group (immediate implant placement in an extraction socket) will be non-inferior to the mean change in crestal bone level for the control group (implant placement in a healed site). | | |
| **Safety** | The subjects will be monitored for adverse events by the investigators until the end of follow-up for each subject. | | |
| **Countries in which the Study will be performed** | United States | | |

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|---|---|
| **Number of participating centers** | 3 centers |
| **Study Principal Investigator** | David L. Cochran, DDS, MS, PhD |
| **Principal Investigators at Centers:** | William Martin, DMD, University of Florida<br>Michael P. Mills, DMD, MS, University of Texas Health Science Center San Antonio<br>Tara Aghaloo, DDS, MD, PhD, University of California at Los Angeles |
| **Number of Subjects** | 52 subjects (randomized 1:1 to test or control) |
| **Estimated Date of Study Initiation** | Q3 2015 |
| **Estimated Date of Study Completion** | Q2 2018 for all subjects to reach the primary endpoint;<br>Q2 2022 for all subjects to complete the follow-up phase. |
| **Sponsor** | Institut Straumann AG |
| **Compliance** | 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).<br>Local legal and regulatory requirements include compliance with 21 CFR 50, 21 CFR 54, and 21 CFR 56. |

## Schedule of Assessments

| Procedures/ Assessments: | Visit 1 | Visit 2a | Visit 2b | Visit 3 | Visit 4[1] | Visit 5[1] | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | Visit 12 | Visit 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit[2] | Tooth Extraction Randomization | Implant Placement | Immediate Post-Op | Uncovering Implant | Implant Loading **Baseline** | Definitive Impression | Final Restoration | 6 month follow-up | Primary Endpoint | Follow-Up | Follow-Up | Follow-Up | Follow-Up |
| | < 45 days prior to Visit 2a | | Immediate or 17 weeks post-extraction | 10 days post-implant placement | 10 weeks ± 3 weeks post-implant placement | 10 weeks ± 3 weeks post-implant placement | 5 weeks post-loading | 10 weeks post-loading | 6 months post-loading | 12 months post-loading | 24 months post-loading | 36 months post-loading | 48 months post-loading | 60 months post-loading |
| Informed consent | X | | | | | | | | | | | | | |
| Inclusion/exclusion | X | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Pregnancy test | X[3] | | | | | | | | | | | | | |
| Med & dental history | X | | | | | | | | | | | | | |
| Full mouth CBCT or panoramic radiograph | X | | | | | | | | | | | | | |
| Periodontal measurements | X | | | | | | | | | X | X | X | X | X |
| Oral hygiene evaluation | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Con. Med. | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Radiographic stent | X | | | | | | | | | | | | | |
| Adverse event check | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tooth Extraction | | X | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Implant placement | | | X | | | | | | | | | | | |
| Suture removal | | | | X | | | | | | | | | | |
| Uncover implant | | | | | X | | | | | | | | | |
| Impression/indexing for provisional fabrication | | | | | X | | | | | | | | | |

| Procedures/ Assessments: | Visit 1 | Visit 2a | Visit 2b | Visit 3 | Visit 4[1] | Visit 5[1] | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 | Visit 12 | Visit 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening Visit[2] | Tooth Extraction Randomization | Implant Placement | Immediate Post-Op | Uncovering Implant | Implant Loading **Baseline** | Definitive Impression | Final Restoration | 6 month follow-up | Primary Endpoint | Follow-Up | Follow-Up | Follow-Up | Follow-Up |
| | < 45 days prior to Visit 2a | | Immediate or 17 weeks post-extraction | 10 days post-implant placement | 10 weeks ± 3 weeks post-implant placement | 10 weeks ± 3 weeks post-implant placement | 5 weeks post-loading | 10 weeks post-loading | 6 months post-loading | 12 months post-loading | 24 months post-loading | 36 months post-loading | 48 months post-loading | 60 months post-loading |
| Temporary prosthesis | | | | | | X | | | | | | | | |
| Impression for definitive fabrication | | | | | | | X | | | | | | | |
| Permanent prosthesis | | | | | | | | X | | | | | | |
| Implant stability – RFA | | | X | | | X | | X | | | | | | |
| Verbal confirmation of pregnancy status, if applicable | | | X | | | X | | | | X | X | X | X | X |
| Peri-apical radiographs | | | X | | | X | | | | X | X | X | X | X |
| CBCT – localized | X[4] | | | | | X | | | | X | X | X | X | X |
| Implant survival | | | | X | X | X | X | X | X | X | X | X | X | X |
| Implant success | | | | | | X | | | | X | X | X | X | X |
| Soft tissue evaluation | | | | | | | | X | | X | X | X | X | X |
| Subject satisfaction | | | | | | | | | | X | X | X | X | X |
| Intra-oral photographs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[1] Uncovering the Implant (Visit 4) and Implant Loading (Visit 5) may be combined at the discretion of the investigator.
[2] The screening assessments can be taken at several visits as long as they are performed within 45 days of the surgery.
[3] The pregnancy test must be administered at screening prior to taking any new radiographs or CBCT scans required for screening.
[4] A localized CBCT is required at screening if a full mouth panoramic radiograph is used at screening instead of the full mouth CBCT.

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# 1 Background and Rationale

Tapered implants (i.e. which have a smaller diameter at the apical part than the crestal part) were introduced primarily to provide better adaptation in immediate extraction sockets. Such implants are designed to engage the socket bone at the apical portion and the alveolar socket walls at the crestal portion. Hypothetically the benefits of this approach are to reduce, or possibly avoid, the need for concomitant bone augmentation procedures and to improve primary stability by engaging more of the socket wall than an equivalent cylindrical shaped implant[1].

Studies that assess potential differences between tapered and cylindrical implants are few, but the limited data available generally suggests similar survival rates,[2] no significant differences in implant stability,[1, 3, 4] and no significant differences in marginal bone loss or bone remodeling between the two implant designs.[5, 6, 7] Several studies have documented the extent of bone remodeling around tapered implants with immediate and early loading[8, 9, 10, 11] and immediate or early placement in extraction sockets.[8, 11,12]

Straumann® has recently introduced the Bone Level Tapered (BLT) implant to the market. It is a solid screw implant comprised of a titanium-zirconium alloy with a SLActive® surface that is large-grit sandblasted and acid-etched. In addition, SLActive® is in a chemically activated state, which is preserved by storage in a physiological NaCl solution. This implant is suitable for oral endosteal implantation in the upper and lower jaw and for the functional and esthetic oral rehabilitation of edentulous and partially dentate patients. Straumann® Bone Level Tapered implants can be used for immediate or early implantation following extraction or loss of natural teeth.

The goal of implant therapy is to provide support for a functional and esthetic restoration with a low risk of complication to the patient. Clinicians have many treatment decisions that impact the successful delivery of functional and esthetic restorations, including timing of implant placement and type of implant. This study will consider the clinical outcomes of using a Straumann® Bone Level Tapered implant for immediate implantation following extraction of natural teeth and compare the outcomes to a more conservative approach of placing the implant in a healed site.

The Proceedings of the Fourth ITI Consensus Conference, sponsored by the International Team for Implantology (ITI), resulted in consensus statements and clinical recommendations focused on clinical and esthetic outcomes of implants placed in post extraction sites. Based on this summary, benefits of immediate placement in extraction sockets (type 1) include extraction and

implant placement in one surgical procedure, reduced overall treatment time, and peri-implant defects usually present as a two- or three- walled defect, allowing for simultaneous bone augmentation.[13] However, it can be technically difficult to prepare the osteotomy to allow for implant placement with primary stability and good prosthetic position. Also, increased risk for mucosal recession may compromise esthetic outcomes, hard and soft tissue augmentation procedures may increase complexity of the case, and bone modeling following tooth extraction can be unpredictable.[13] A recent study found that three months following final crown delivery, there were no significant differences in esthetic, clinical and patient-centered outcomes following type 1 and type 2 (defined as implant placement after 4-8 weeks of healing) implant placement. Short term results suggest that one may achieve good optimal esthetic and clinical results with these placement protocols and Straumann titanium Bone Level Implants with the SLActive surface[14].

This randomized, controlled, multi-center study will evaluate the clinical and radiographic outcomes of immediate placement of the Straumann® Bone Level Tapered implant in extraction sockets and will compare these outcomes to those obtained when placing the implant in healed sites. This study will provide data to help guide clinicians when deciding on timing of implant placement and how this impacts implant stability and the ability to provide a functional and esthetic restoration for the patient.

## 2 Study Objectives

The aim of this randomized, controlled, multi-center study is to assess the clinical and radiographic outcomes of using a Straumann® Bone Level Tapered implant for immediate implantation following extraction of a tooth in the pre-molar and anterior region of the maxilla and mandible (**test**) compared to the outcomes of placing this implant in similarly located healed sites (**control**). All implants will be loaded early at 10 to 12 weeks.

The **primary objective** is to demonstrate that the change in mean peri-implant marginal bone level changes (mesial and distal) from loading to 12 months post-loading of the test treatment will be no worse than the control treatment.

The **secondary objectives** of the study are to assess differences in clinical and radiographic outcomes between the test and control treatment groups by looking at implant success and survival, buccal bone dimensional changes, implant stability, soft tissue changes, subject satisfaction and adverse events.

An **additional objective** is to assess long-term differences in clinical and radiographic outcomes, as measured in the primary and secondary objectives, over the span of five years.

# 3 Study Design

## 3.1 Type and Design of Study

This study is a post-market, randomized, controlled, multi-center clinical study.

## 3.2 Indications for Use

Straumann® dental implants are indicated for oral endosteal implantation in the upper and lower jaw and for the functional and esthetic oral rehabilitation of edentulous and partially dentate patients. Straumann® dental implants can also be used for immediate or early implantation following extraction or loss of natural teeth. Implants can be placed with immediate function on single-tooth and/or multiple tooth applications when good primary stability is achieved and with appropriate occlusal loading, to restore chewing function. The prosthetic restorations used are single crowns, bridges and partial or full dentures, which are connected to the implants by the corresponding elements (abutments). The complete details of the instructions for use for the Straumann® Bone Level Tapered Implant can be found in the Instructions for Use IFU (Appendix 1).

***Warnings:***

*Products must be secured against aspiration when handled intraorally. Aspiration of products may lead to infection or unplanned physical injury.*

*Avoid approaching the proximity of the mandibular nerve channel during implant bed preparation and implant insertion. Nerve damage may result in anesthesia, paresthesia and dysthesia.*

***Cautions/Precautions:***

*Always select the largest diameter implant that can be supported by the available bone thickness, bone quality, inter-dental spacing, and anticipated mastication forces. Particular care should be taken to assure proper implant alignment when comparatively high loads are expected. Small-diameter implants are not recommended for the posterior region.*

*A careful clinical and radiological examination of the patient should be performed prior to surgery to determine the psychological and physical status of the patient. Special attention should be given to patients who have local or systemic factors that could interfere with the healing process of either bone or soft tissue or the osseointegration process (e.g. bone metabolism disturbances, previously irradiated bone in the head or neck area, diabetes mellitus, anticoagulation drugs/hemorrhagic diatheses, bruxism, parafunctional habits, unfavorable anatomic bone conditions, tobacco abuse, untreated periodontal disease, acute infection of implant site, temporomandibular joint disorders, treatable pathologic diseases of the jaw and changes in the oral mucosa, pregnancy, inadequate oral hygiene).*

*Sterile handling is essential. Never use potentially contaminated components. Contamination may lead to infections.*

*The implants must be stored in a dry place in the original packaging, protected from direct sunlight and at room temperature. Improper storage may compromise essential material and design characteristics leading to device failure.*

*Do not re-sterilize Straumann dental implants. Cleaning, disinfection and sterilization may compromise essential material and design characteristics leading to device failure.*

*Do not re-use Straumann Dental implants. Re-use of single-use devices creates a potential risk of patient or user infections.*

*Avoid corrections of the vertical position using reverse rotations (counterclockwise). This can cause loosening of the screw-retained transfer piece and may lead to decreased primary stability.*

## 3.3 Study Treatments

Subjects needing a single tooth extraction and replacement with a dental implant in the anterior or pre-molar region of the maxilla or mandible will be screened to determine study eligibility. Following tooth extraction, the inclusion and exclusion criteria will be re-evaluated, and if the subject continues to be eligible, the surgeon will proceed with randomization, bone grafting of the extraction socket with Straumann allograft and implant placement. Subjects randomized into the test group will receive bone grafting of the extraction socket and an implant during the same surgical procedure as the tooth

extraction. Subjects randomized into the control group will also undergo bone grafting of the extraction socket with Straumann allograft and eturn for a second surgery after 4 months of healing.

After randomization the subject is considered enrolled in the study.

Ten days following implant placement, subjects will be evaluated for healing and possible suture removal in cases when non-resorbable sutures are used. The subject will return in 8 weeks following implant placement to uncover the implant. An index or impression will be taken for provisional fabrication. Contingent upon good primary stability, the implant will be loaded in appropriate occlusion with an abutment and temporary prosthesis at 10-12 weeks post implant placement. Note that implant loading may be done at the same visit as uncovering the implant at the discretion of the investigator.

The definitive impression will be taken at 4-6 weeks following implant loading and the final prosthesis will be seated at 8-12 weeks following implant loading.

## 3.4 Primary Endpoint

Mean crestal bone level change from implant loading to 12 months post-implant loading will be measured as the primary endpoint. Crestal bone levels on both the mesial and distal aspect of the implant will be averaged to calculate the crestal bone level.

## 3.5 Secondary Endpoints

The following parameters will be measured as secondary endpoints 12 months post-implant loading:

- Implant success and survival
- Buccal bone dimensional changes measured on cone beam computed tomography (CBCT) images
- Implant stability measured by resonance frequency analysis (RFA) at implant placement, implant loading and final restoration
- Changes in soft tissue (gingival and papilla margins – baseline at final restoration)

- Subject satisfaction (esthetics, function, and level of pain)
- Adverse Events (AEs) and Adverse Device Effects (ADEs) incidence

## 3.6 Additional Analysis

An additional analysis will be conducted at 24, 36, 48, and 60 months post-implant loading and the following will be measured:

- Mean crestal bone level changes
- Implant success and survival
- Dimensional changes of the buccal bone as measured on CBCT images
- Changes in soft tissue (gingival and papilla margins)
- Subject satisfaction (esthetics, function, and level of pain)
- Adverse events and adverse device effects incidence

## 3.7 Study Sample Size

The study will enroll and randomize 52 subjects at two research centers. The subjects will be randomized 1:1 to either receive the test treatment or the control treatment. The enrollment will be capped at 30 subjects at each site.

## 3.8 Study Duration

The study is expected to enroll a maximum of 52 subjects over a 12 months period. Subjects randomized to the test group will be followed for 63 months (3 months to reach implant loading, then 12 months to reach the primary endpoint, followed by another 48 months of long term follow-up). Subjects randomized to the control group will be followed for 67 to 67.5 months (4 to 4.5 months healing prior to implant placement, 3 months to reach implant loading, then 12 months to reach the primary endpoint, followed by another 48 months of long term follow-up. The total duration of the study is expected to span anywhere from 79 to 79.5 months.

## 3.9 Study Population

The study population will consist of male or female subjects, 18 years of age or older, who are in need of a single tooth extraction in the pre-molar or anterior region of the maxilla or mandible and who meet the inclusion/ exclusion criteria. Subjects will be recruited through the clinics where the investigators are practicing and possibly through referring dentists.

Subjects are permitted to have multiple teeth extractions and/or receive multiple implants during the surgical procedure, however only one of the implants will be defined as the study implant. In the case of multiple implants, the study implant site will be selected by the investigator prior to implant placement based on which site fits the inclusion/exclusion criteria.

Those subjects who appear eligible according to the inclusion and exclusion criteria will be asked to provide informed consent in writing prior to any study related procedures and will be considered "consented" in the study. Subjects will be evaluated based on the inclusion and exclusion criteria for initial eligibility during the screening visit and re-evaluated after tooth extraction. Once the subject is randomized, he/she is considered "enrolled" in the study and it will be documented in the enrollment log. Subjects who undergo tooth extraction, but are not eligible to be randomized, will be considered screen failures.

### 3.9.1 Inclusion Criteria

All of the criteria must be met to receive the study implant:

- Subjects must have voluntarily signed the informed consent form before any study related procedures
- Subjects must be males or females who are a minimum of 18 years of age
- Subjects who are in need of a single tooth extraction in the pre-molar or anterior region of the maxilla or mandible (ADA tooth positions 4-13 and 20-29) and replacement with a dental implant.
- Implants must be placed either immediately in an extraction socket or placed in a healed site (greater than 4 months healing) which has not been previously grafted.

- Planned site for implant must have a natural tooth both mesially and distally in the adjacent tooth positions
- Subjects must have opposing dentition (natural teeth, fixed or removable restorations)
- There must be sufficient bone at the implant site to achieve primary stability based on evaluation of bone from the CT scan and clinical assessment at the time of implant
- 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

### 3.9.2 Exclusion Criteria

If any of the following are met prior to receiving the implant, the subject must be excluded from the study.

- Subjects with a systemic disease that would preclude dental implant surgery
- Subjects with any contraindications for oral surgical procedures
- Subjects with mucosal diseases (e.g., erosive lichen planus) in the localized area around the study implant site
- Subjects with a history of local irradiation therapy in the head/neck area
- Subjects with any untreated endodontic lesions or untreated periodontal disease adjacent to the implant site
- Subjects receiving, or having a history of receiving, intravenous or subcutaneous antiresorptive agents, such as bisphosphonates
- Subjects with severe bruxing, parafunctional habits, or temporomandibular joint dysfunction
- Any implant sites where there will be a buccal dehiscence greater than 3 mm or there will be a fenestration of the implant
- Subjects with inadequate oral hygiene or who are unmotivated for adequate home care

- Subjects who have physical or mental handicaps that would interfere with the ability to perform adequate oral hygiene
- Subjects who are pregnant or intending to become pregnant during the duration of the study
- Subjects who are heavy smokers (defined as >10 cigarettes per day or >1 cigar per day) or chew tobacco
- Subjects who abuse alcohol or drugs
- Subjects who have undergone administration of any investigational device within 30 days of enrollment in the study
- 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, such as history of non-compliance or unreliability

# 4 Device Description

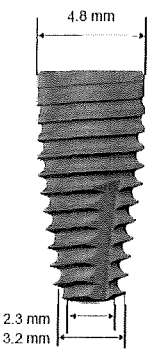
Specified devices and products to be used in this study will be provided by Straumann USA, LLC.

## 4.1 Study Product

### 4.1.1 General Description of the Study Implant

The complete details of the product description and instructions for use for the Straumann® Bone Level Tapered implant can be found in the instructions for use (Appendix 1). The implants are available with an endosteal diameter of 3.3 mm, 4.1 mm or 4.8 mm and lengths of 8, 10, 12, 14 and 16 mm. They are designed to be placed at bone level. They are made of a binary titanium-zirconium alloy called Roxolid® and have the SLActive® surface which is a large grit sandblasted and acid-etched surface in a chemically activated state. The chemically activated state is preserved by storage in a physiological sodium chloride solution.

The following Bone Level Tapered implants will be available for use in this study:

| Material: | Roxolid® | | |
|---|---|---|---|
| Surface: | SLActive® | | |
| Diameter: | 3.3 mm | 4.1 mm | 4.8 mm |
| |  |  |  |
| **Length:** | **Article Numbers:** | | |
| 8 mm | 021.3308 | 021.5308 | 021.7308 |
| 10 mm | 021.3310 | 021.5310 | 021.7310 |
| 12 mm | 021.3312 | 021.5312 | 021.7312 |
| 14 mm | 021.3314 | 021.5314 | 021.7314 |
| 16 mm | 021.3316 | 021.5316 | 021.7316 |

### 4.1.2 Restorative Components

The clinician may select the appropriate restorative components for the case from any of the Straumann® restorative components available for the Straumann® Bone Level Tapered implants.

## 4.2 Instructions for Use, Handling, and Labeling

Straumann® will provide the two centers with the necessary amount of study products for the study. The products delivered for the study are to be used only for the subjects enrolled in the study and according to the clinical investigation plan.

The study product will be used as described in the instructions for use (Appendix 1 – IFU 701351). The implants are CE marked and subject of FDA cleared 510(k) pre-market notifications (K140878). The associated prosthetic components for the implant are also CE marked and subjects of FDA cleared 510(k) pre-market notifications (K130808, K122192, K092814, K093027, K072497, K070549, K110580, K091701, K071357, K062129,

K080286, K072071, K081005, K072151, K120822, K132219,). The products must be used within their cleared indications.

All device deficiencies shall be reported by the investigator to Straumann USA on a Device Deficiency Case Report Form.

## 4.3 Storage

The study product should be stored in its original container until used and its access shall be controlled.

After treatment of the last subject, any remaining unopened study products must be returned to Straumann® and acknowledged for receipt. The investigator must maintain an accurate and up-to-date accountability record of all study products received, used, discarded (opened, but non-used) and returned during the course of the study. At each monitoring visit, the monitor will check the investigational device accountability for accuracy and completeness.

## 4.4 Device Accountability

The Investigator must maintain an accurate and up-to-date accountability record of all study products 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 File.

## 4.6 Risk Analysis, Risk/ Benefits

The device risk analysis and risk assessment for the Bone Level Tapered implants was conducted according to EN ISO 14971 for CE marked implants. Full results are included in the Risk Management Report dated 9 May 2014.

Refer to the Section 7.2.5 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 (IFU 701351) under Warning and Cautions/ Precautions.

There is a residual risk of aspiration/swallowing of the device if the implant is removed once it has been seated to 35 Ncm (e.g. incorrect implant bed preparation). This reduces the retention force of the Loxim transfer piece in the implant and may cause it to fall off once it is out of the implant bed. Based on the current information from the field and continuous improvement of the design, it is decided that this residual risk is acceptable. Justification: the majority of surgeons are using the handpiece to insert a dental implant, at least until the last final turns. The reason to remove the implant while inserting it could be due to hard bone, under-preparation or too high torque. In this case the implant is removed well before the final seating. Removing the implant after it is fully seated is unlikely and seen by the surgeons as an exceptional situation, requiring extra attention. Therefore, the risk of occurrence of low retention force is outweighed by the benefit of achieving primary stability.

An anticipated benefit of immediate implant placement with early loading is that extraction and implant placement can be performed in one surgical procedure, thereby reducing the overall treatment time and possibly allowing simultaneous bone augmentation.

# 5 Study Procedures

## 5.1 Subject Enrollment and Evaluation

### 5.1.1 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations) to obtain informed consent in writing 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 must 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, or benefits of the study. The investigator or designee must 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 must be approved by an Institutional Review Board (IRB) before consenting can begin. The informed consent form must be available in the primary language of the subject. It is written in accordance with the "Declaration of Helsinki" (as adopted by the 18th World Medical Assembly, 1964, and as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008), and Fortaleza (2013) (Appendix 2)) and applicable local regulations.

This IRB approved consent form must be personally signed and dated by the subject and the person obtaining consent. Investigators should keep the original signed informed consent document in a secure location. A copy of the signed consent form should be given to the subject. The Case Report Forms (CRFs) for this study contain a section for documenting informed consent, and this must be completed appropriately.

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 should be informed of the new information, given a copy of the revised form and give their consent to continue the study, unless the subject signed consent and was considered a screen failure.

### 5.1.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be evaluated according to Sections 3.9.1 and 3.9.2 at the screening visit. The inclusion and exclusion criteria should be re-evaluated at Visit 2a after tooth extraction and prior to randomization. Subjects must fulfill all of the inclusion criteria and not meet any of the exclusion criteria to be eligible for enrollment in the study.

### 5.1.3 Demographics

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

### 5.1.4 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 screening, before taking any new radiographs or CBCT scans required at screening, 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. A woman of child-bearing potential will be asked to verbally confirm that she is not pregnant at visits requiring either peri-apical radiographs or CBCT scans.

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 periapical radiographs or CBCT, and the outcome of the pregnancy should be documented.

### 5.1.5 Medical and Dental History

The dental history will be obtained at the screening visit. The dental history should include dental status information including a description of the opposing and adjacent dentition, history of smoking status, and an oral exam.

Relevant medical history (e.g., 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.

### 5.1.6 Screening CBCT or Panoramic Radiograph

A panoramic radiograph or full mouth CBCT scan must be available during screening to assess the complete dentition and to use in surgical planning. The screening panoramic radiograph or full mouth CBCT scan can be taken during the screening visit or be available from a previous date within 6 months of the implant surgery. If a panoramic radiograph is used for screening, then a localized CBCT scan is also required as a baseline.

### 5.1.7 Periodontal Measurements

All periodontal measurements will be performed using a manual, millimeter calibrated periodontal probe (UNC 15, Hu-Friedy, Chicago, IL, USA). The periodontal measurements will be used to assess the periodontal health of the area surrounding the dental implant. These measurements will be recorded at screening and at 12, 24, 36, 48, and 60 months post loading.

*Modified Sulcus Bleeding Index (mSBI):*

It will be documented if bleeding is induced at the marginal gingival tissue by running a blunt periodontal probe along the soft tissue wall at the orifice of the pocket. The bleeding tendency will be evaluated on the two adjacent teeth at 6 locations (distofacial, facial, mesiofacial, distolingual, lingual, mesiolingual) and assessed using the mSBI by Mombelli et al.[15]

- Score 0: No bleeding when a periodontal probe is passed along the gingival margin
- Score 1: Isolated bleeding spots visible
- Score 2: Blood forms a confluent red line on margin
- Score 3: Heavy or profuse bleeding

*Probing Pocket Depth (PPD):*

The PPD will be measured at the two adjacent teeth by recording the distance from the gingival margin to the bottom of the probable pocket at six locations (distofacial, facial, mesiofacial, distolingual, lingual, mesiolingual).

### 5.1.8 Oral Hygiene Evaluation

The subject's overall oral hygiene will be evaluated at each study visit starting with the screening visit by choosing one of the following: "excellent", "good", "fair", or "poor".

### 5.1.9 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. All prophylactic antibiotics and anesthesia given must be recorded on the Concomitant Medication Form. This includes the pre-rinse with chlorhexidine mouthwash 0.12% for 30 seconds immediately prior to the surgery.

### 5.1.10 Fabrication of Radiographic Stent

A radiographic stent will be fabricated at screening. The stent should be fabricated according to the instructions provided in the Operations Manual.

### 5.1.11 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 descried 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 Surgical Procedure and Outcome Assessments

### 5.2.1 Surgery/ Tooth Extraction

Each subject will have a tooth extracted using standard procedures in an outpatient environment under local anesthesia and sedation as indicated. Subjects will pre-rinse with chlorhexidine mouthwash 0.12% for 30 seconds immediately prior to the surgery.

### 5.2.2 Randomization

All eligible subjects will be randomized at each center in a 1:1 ratio to one of the two treatment groups at the time of surgery. Immediately after tooth extraction and confirmation of inclusion and exclusion criteria, the study coordinator or surgical assistant will log into the Electronic Data Capturing (EDC) system to determine the treatment group assignment. Further treatment will continue based on the randomization assignment.

The treatment group will be assigned to subjects in the chronological order in which they were enrolled using a computer generated randomization schedule stratified by study center and prepared by an independent randomization statistician. Although this study is not blinded, no access to the randomization logic will be available to the study center, study subjects, or employees of Straumann.

In the event that more than one implant can be placed for a subject according to the study indication, only one implant will be defined as the study implant and randomized to a treatment group. The study implant site will be selected by the Investigator prior to surgery, based on an evaluation of which implant site fits the inclusion/exclusion criteria.

### 5.2.3 Surgery/ Implant Placement

Each subject will receive the study device using standard implant placement procedures which will be performed in an outpatient environment. Surgery is performed under local anesthesia and sedation as indicated following standard surgical and sterile techniques. For additional information, consult the current Straumann procedure guides and Instructions for Use for detailed procedures relating to implant bed preparation and implant placement. Prophylactic antibiotic treatment may be given at the discretion of the investigator according to the investigator's standard practice.

All prophylactic antibiotics and anesthesia given must be recorded on the Concomitant Medication Form. Prior to surgery subjects should have teeth cleaned if required as per standard of care at the practice.

Bone grafting of the extraction socket must be performed on both subjects randomized to immediate placement and those randomized to delayed placement. Guided Bone/Tissue Regeneration (GBR/GTR) procedures according to the investigator's standard practice may also be performed at implant placement for esthetic, contour augmentation or to augment minimal buccal dehiscence defects less than 3 mm. The size of the defect around the implant must be measured prior to the augmentation procedure utilizing a periodontal probe, including defect height, infra-bony defect, defect width, and defect depth. For both socket grafting and GBR for contour augmentation, only Straumann allograft will be used.

The following is a detailed list of the procedures and measurements during the implant surgery:

- Subjects will pre-rinse with chlorhexidine mouthwash 0.12% for 30 seconds immediately prior to the surgery (subjects in control group only).
- For subjects in the immediate placement group, the implant will be placed in the same procedure as the tooth extraction. Extract tooth and determine the location of the implant site. For subjects in the delayed placement, raise the flap.
- Take measurements at the implant site including the orafacial ridge width and mesiodistal width at crestal bone level.
- Prepare the implant bed according to the standard drilling sequence and based on the bone class. The profile drill and tapping may be recommended. Record the bone quality at the implant site (i.e., Type I to Type IV bone). Note the final drill and whether it was used to depth.
- Bone grafting of the extraction socket.
- Place the implant into the site according to standard procedures and record the implant size and lot number, along with the insertion torque value. Evaluate if

primary stability was achieved and measure the Implant Stability Quotient (ISQ).

- Attempt a semi-submerged healing with tissue adapted and sutured over a small cover screw. Suture material will be left to the discretion of the investigator but documented in the case report form.
- Record if a bone regeneration procedure was necessary for a minimal dehiscence less than 3 mm and note the bone substitutes or barriers used in the procedure. Also record if soft or hard tissue contour augmentation was performed.
- The Investigator may prescribe Chlorhexidine rinse in addition to medications for infection control and post-operative pain control according to his/her standard practice. Instructions on proper post-operative oral hygiene, routine cleaning and maintenance should be provided as required by standard of care.

### 5.2.4 Implant Stability by Resonance Frequency Analysis (RFA)

An Osstell device is an instrument that uses the RFA method to determine implant stability and osseointegration. The result is presented as an Implant Stability Quotient (ISQ) value of 1 – 100. The higher the ISQ, the more stable the implant. Additional information about the Osstell device can be found at www.osstell.com. Instructions on taking the measurements for this protocol will be provided in the Operation Manual. In general two measurements will be taken from two different angles at implant placement, implant loading, and final restoration.

### 5.2.5 Standardized Peri-apical Radiographs

Standardized peri-apical radiographs of the area being treated will be taken post-operatively, at implant loading, and at 12, 24, 36, 48, and 60 months post-loading. The radiographs must be of high quality and definition, so as to identify the bone contours in question. Ideally the entire implant should be visible on the radiograph. However it is not essential that the apical end of the implant is on the radiograph; in this case at least three threads must be visible on the radiograph. These radiographs will be used for crestal bone level assessment and evaluation of implant success.

Radiographs will be digital, using either a direct sensor system or an indirect system with Photostimulable Phosphor (PSP) plate. A stent is to be used. All settings must be noted and utilized on subsequent visits.

To standardize the series of periapical radiographs, the same sensor/phosphor plate holder and beam aiming device will be used throughout the study (e.g., Rinn System). The radiographs will be taken with the sensor/phosphor plate placed parallel to the implants and the X-ray beam directed perpendicular to the implants. The digital image should be saved as a JPEG file and the file name should be formatted as follows: Subject number (XX-XX)_Subject initials (XXX)_Image date (DD MMM YYYY), i.e., 01-01_ABC_04 Nov 2014.jpg

The files will be uploaded into the Electronic Data Capture system.

### 5.2.6 Marginal Bone Level Changes

Bone level changes will be evaluated on a standardized peri-apical radiograph at implant loading and at 12, 24, 36, 48, and 60 months post-loading. The radiographs will be sent to a centralized location to be evaluated in a blinded fashion by a single reader using a calibrated measuring tool. Additional details will be provided in operations manual to describe how the central radiologist will measure the bone level values from the radiographs.

### 5.2.7 Buccal Bone Dimensional Changes

Cone beam computed tomography will be utilized to measure the dimensional thickness of buccal plate of the localized area around the implant at screening, implant loading and at 12, 24, 36, 48 and 60 months post-loading. Additional details will be provided in operations manual to describe how the central radiologist will measure the bone level values from the CBCT scans.

### 5.2.8 Implant Success and Survival

Implant survival will be assessed at all visits following the surgical visit. A surviving implant is an implant that is in place at the time of follow-up.

Implant success will be assessed at implant loading, and at 12, 24, 36, 48, and 60 months post loading. A successful implant will meet all of the following criteria according to Buser[16]:

- Absence of persistent subjective complaints, such as pain, foreign body sensation, and/ or dysesthesia
- Absence of a recurrent peri-implant infection with suppuration
- Absence of mobility
- Absence of a continuous radiolucency around the implant

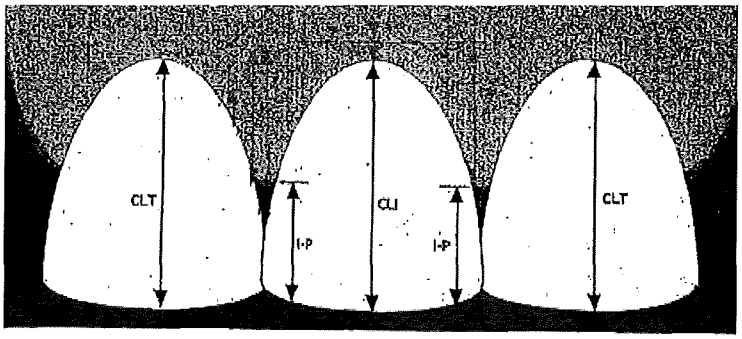
Non-surviving implants will be counted as an unsuccessful implant.

Any dental implant showing excessive bone loss, radiolucency, or infection shall be treated in the manner best suited to the well-being of the subject, including treatment to save the dental implant. Continuous radiolucency, implant mobility, and recurrent peri-implant infection with suppuration shall be recorded on the adverse event form (see section 7.3.4).

### 5.2.9 Soft Tissue Evaluation

Gingival recession and papilla height will be evaluated according to Grunder[17], recording changes in gingiva/mucosa and papilla margins over time. The soft tissue will be evaluated at final restoration, and at 12, 24, 36, 48, 60 months post-implant loading. The following measurements will be recorded in millimeters:

- Measurement $CLT_m$ and $CLT_d$ – length of the crown from highest point of soft tissue margin to the incisal edge of the adjacent mesial and distal teeth
- Measurement CLI – length of the implant crown from highest point of the soft tissue margin to the incisal edge
- Measurement $IP_m$ and $IP_d$ – distance from the top of the papilla to the incisal edge mesial and distal of the implant crown




### 5.2.10 Subject Satisfaction

Subject satisfaction will be assessed utilizing Visual Analogs Scales (VAS) at 12, 24, 36, 48, and 60 months post implant loading for the following parameters related to the implant and restoration:

- Level of pain associated with the implant and crown – Painful → No pain
- Level of satisfaction with the function of the implant supported crown - Not satisfied at all → Highly satisfied
- Level of satisfaction with the esthetics of the implant supported crown - Not satisfied at all → Highly satisfied

Each subject will be asked to complete a VAS for each of the above parameters by the Investigator. The subject will be given a paper questionnaire to mark their responses on the VAS (Appendix 3). The subject will mark a 100 mm scale with a vertical line. A measurement will be made from the left on the scale to the point of the first marking from the subject. This measurement will be recorded on a case report form.

### 5.2.11 Intra-Oral Photographs

Intra-oral photographs will be taken at each study visit to show the pre-operative situation, the implant in place in the bone at surgery, the temporary restoration, the final restoration and the final crown at all follow-up visits. Additional photographs are optional and can be taken to fully document the case.

Each photograph should be labeled with the subject's study identification number and visit date.

## 5.3 Protocol Related Procedures

### 5.3.1 Screen Failures

Any subject that signs the Informed Consent Form must be entered into the electronic database. Subjects will be evaluated based on the inclusion and exclusion criteria for initial eligibility during the screening visit and re-evaluated after tooth extraction. Any subjects that are determined to be ineligible prior to be randomized, will be considered screen failures. Screen failures will be documented by completing a Screen Failure Case Report Form.

### 5.3.2 Early Withdrawal

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 (SAE) or adverse event, which in the opinion of the Investigator prevents the subject's further participation in the study.
- Failure to achieve primary stability – if primary stability is not obtained and the implant is removed, the patient will be withdrawn at the time of implant removal. No further follow up is necessary.
- No study implant placed – if the study implant is never placed, regardless of reason, the patient will be withdrawn. No further follow up is necessary.

The subject withdrawal will be documented on a Study Termination/ End of Study CRF and must include the reason for the subject withdrawal. Efforts should be made to capture the primary study endpoint for each subject prior to withdrawal, if possible. If the subject fails to attend follow-up visits, at least three attempts to reach the subject must be documented; with at least one of the attempts made by certified letter.

**Withdrawn subjects will not be replaced.**

### 5.3.3 End of Study

Once the subject is seen for the final visit at 60-months post-loading, the subject will have completed the study. This will be documented on a Study Termination/ End of Study CRF.

### 5.3.4 Subject Replacement Policy

Subjects who have been randomized will not be replaced.

### 5.3.5 Protocol Deviations

Deviations from the procedures established in the protocol are not permitted. If a deviation occurs, the study center must record the deviation on the appropriate CRF. The sponsor shall be notified immediately of any deviations in informed consent, inclusion/exclusion criteria, and randomization procedures. The IRB should be notified according to the requirements of the local IRB.

Any deviation from the protocol (including deviations from the expected study visit windows) 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 a table format after the protocol synopsis.

### 6.1 Visit Windows

Subjects need to be seen within the following windows:

| Visit # | Visit Name | Visit Window |
|---|---|---|
| Visit 1 | Screening | < 45 days from tooth extraction |
| Visit 2a | Tooth Extraction and Randomization<br>Bone grafting of the extraction socket | |
| Visit 2b | Implant Surgery | Immediately at tooth extraction<br>or<br>17 weeks ± 1 weeks after tooth extraction |

| | | |
|---|---|---|
| Visit 3 | Immediate Post-Operative | 10 days ± 3 days after implant surgery |
| Visit 4* | Uncover Implant | 10 weeks ± 3 weeks after implant surgery |
| Visit 5* | Implant Loading/ Temporary Restoration | 10 weeks ± 3 weeks after implant surgery |
| Visit 6 | Impression | 5 weeks ± 1 week post-loading |
| Visit 7 | Final Restoration | 10 weeks ± 2 week post-loading |
| Visit 8 | 6-month follow-up | 6 months ± 1 month post-loading |
| Visit 9 | Primary Endpoint | 12 months ± 1 month post-loading |
| Visit 10 | Additional follow-up | 24 months ± 1 month post-loading |
| Visit 11 | Additional follow-up | 36 months ± 1 month post-loading |
| Visit 12 | Additional follow-up | 48 months ± 1 month post-loading |
| Visit 13 | Additional follow-up | 60 months ± 1 month post-loading |

*Note: Uncovering the implant and implant loading may be done at the same visit at the discretion of the investigator.

## 6.2 Visit 1 - Screening Visit

This visit should be completed within 45 days prior to the tooth extraction (Visit 2a). An initial evaluation will be conducted to determine whether the subject meets the study inclusion and exclusion criteria and for collection of baseline data. This evaluation will include an appropriate medical and dental history, a clinical examination, and a radiographic evaluation. The screening evaluations and data collection can take place at several office visits as long as the visits are within 45 days of the surgery.

If the screening evaluations are not conducted within 45 days of the surgery, then the subject may be asked to re-consent and re-screen, as long as enrollment is still open.

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

- Informed consent
- Inclusion/exclusion criteria
- Demographics
- Pregnancy test (administered prior to randomization and before taking study required radiographs or CBCT scans)

- Medical and dental history
- Full mouth CBCT or panoramic radiograph with a localized CBCT scan
- Periodontal measurements (PPD and mSBI at adjacent teeth)
- Oral hygiene evaluation
- Concomitant medications
- Adverse event check
- Radiographic stent fabrication
- Intra-oral photographs

## 6.3 Visit 2a – Tooth Extraction/ Randomization

The following will be performed at this visit:

- Review inclusion/exclusion criteria
- Oral hygiene evaluation
- Concomitant medication
- Adverse event check
- Surgery/ tooth extraction
- Bone grafting of the extraction socket
- Randomization
- Intra-oral photographs

## 6.4 Visit 2b – Implant Surgery

The timing of Visit 2b will depend on the treatment group assigned during randomization. For subjects randomized to the test group, the implant will be placed immediately after tooth

extraction and bone grafting of the extraction socket. For subjects randomized to the control group, the extraction socket will be bone grafted but allowed to heal for at least 4 months. Straumann allograft will be used for all socket grafting. The subject should return for Visit 2b implant surgery, at 17 weeks (± 1 week).

- Review inclusion/exclusion criteria
- Oral hygiene evaluation
- Concomitant medication
- Adverse event check
- Surgery/ bone grafting of extraction socket/implant placement
- Implant stability by RFA
- Verbal confirmation of pregnancy status, if applicable
- Standardized periapical radiographs
- Intra-oral photographs

## 6.5 Visit 3 - Immediate Post-Operative

The subject will be recalled for a post-operative visit at 10 days (± 3 days) following implant placement for a general assessment of wound healing and to remove sutures, if applicable.

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

- Suture removal, if necessary
- Oral hygiene assessment
- Concomitant medication
- Adverse event check

- Implant survival
- Intra-oral photographs

## 6.6 Visit 4 – Uncovering Implant

At 10 weeks (± 3 weeks) following implant surgery, the implant will be uncovered, a healing abutment placed, and the soft tissue adapted around the healing abutment. Note that implant loading (Visit 5) may be done at Visit 4 at the discretion of the investigator.

- Uncover implant, place healing abutment
- Impression or indexing the implant for indirect provisional fabrication
- Oral hygiene assessment
- Concomitant medication
- Adverse event check
- Implant survival
- Intra-oral photographs

## 6.7 Visit 5 – Implant Loading (BASELINE)

At 10 weeks (± 3 weeks) after implant surgery (2 - 4 weeks after uncovering the implant), and contingent upon good primary stability, the study implant will be loaded with a temporary abutment and restoration in appropriate occlusion. Note that uncovering of the implant (Visit 4) and implant loading can be done at the same visit at the discretion of the investigator.

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

- Temporary prosthesis seated
- Oral hygiene evaluation

- Concomitant mediation
- Adverse event check
- Implant stability by RFA
- Verbal confirmation of pregnancy status, if applicable
- Standardized periapical radiographs
- CBCT - localized
- Implant survival and success
- Intra-oral photographs

## 6.8 Visit 6 – Definitive Impression

At 5 weeks (± 1 week) post loading, an impression (digital or conventional) will be taken for the fabrication of the final restoration.

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

- Impression for definitive fabrication
- Oral hygiene evaluation
- Concomitant mediation
- Adverse event check
- Implant survival
- Intra-oral photographs

## 6.9 Visit 7 - Final Restoration

Subjects will be recalled at 10 weeks (± 2 weeks) post loading to seat the final restoration.

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

- Permanent prosthesis seated
- Oral hygiene evaluation
- Concomitant medication
- Adverse event check
- Implant stability by RFA
- Implant survival
- Soft tissue evaluation
- Intra-oral photographs

## 6.10 Visit 8 – 6 Month Follow-Up

Subjects will be recalled at 6 months (± 1 month) for brief evaluation of the implant supported final restoration and check possible adverse events.

- Oral hygiene evaluation
- Concomitant medication
- Adverse event check
- Implant survival
- Intra-oral photographs

## 6.11 Visit 9 – 12 Month Follow-Up

Subjects will be recalled at 12 months (± 1 month). Primary and secondary endpoints will be evaluated at this visit.

- Periodontal measurements (PPD and mSBI at adjacent teeth)

- Oral hygiene evaluation
- Concomitant mediation
- Adverse event check
- Verbal confirmation of pregnancy status, if applicable
- Standardized periapical radiograph
- CBCT – localized
- Implant survival and success
- Soft tissue evaluation (gingival margin and papilla height)
- Subject satisfaction
- Intra-oral photographs

### 6.12 Visits 10, 11, 12, and 13 - Follow-Up Visits

Subjects will be recalled at 24 months (± 1 month), 36 months (± 1 month), 48 months (± 1 month), and 60 months (± 1 month) post loading. Data from these visits will be used for the additional analyses.

- Periodontal measurements (PPD and mSBI at adjacent teeth)
- Oral hygiene evaluation
- Concomitant mediation
- Adverse event check
- Verbal confirmation of pregnancy status, if applicable
- Standardized periapical radiograph
- CBCT – localized

- Implant survival and success
- Soft tissue evaluation (gingival margin and papilla height)
- Subject satisfaction
- Intra-oral photographs

# 7 Evaluation of Adverse Events

For the avoidance of doubt, ***all*** AE/SAEs as defined below, **regardless of whether they are related to the investigational device**, should be collected, fully investigated and documented in the source document and appropriate case report form for all subjects from the time of the signing of the informed consent until the last protocol-specific procedure. Documentation includes dates of event, treatment, outcome, assessment of seriousness and causal relationship to the device and/or study procedure (rationale to be provided).

## 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
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or

- 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

NOTE: 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. DDs 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 will be classified as an 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>
<tr><th>Adverse events</th><th>Non-device related</th><th colspan="2">Device or procedure related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="2">Serious</td><td rowspan="2">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated<br>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated<br>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</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, outcome, 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 implanted product (e.g., dental implant) and provide the rationale in a short narrative. 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 causal and temporal 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** – A causal relationship with device application can be definitely excluded. By definition, all AEs/ADEs, with a start date before the surgery procedure at Visit 2 must be assigned a "not related" relationship with study device.

NOTE: Device deficiencies that might have led to an SAE are always related to the medical device.

### 7.2.3 Relationship to the Procedure

The investigator should assess the relationship of the adverse event to the implant procedure (e.g. placement of dental implant) and provide the rationale in a short narrative. The relationship should be assessed using the categories described in Section 7.2.2.

### 7.2.4 Severity

Each adverse event should be assessed by the investigator 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; the event is easily tolerated by the subject
- **Moderate** – discomfort sufficient enough to reduce or affect normal daily activity
- **Severe** – Inability to work or perform normal daily activity and/or the subject's life is at risk from the adverse event

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** - 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 table below presents the potential expected adverse device effects following the insertion of dental implants.

Table: List of expected ADEs following the insertion of dental implants:

| **Biological complications** | | |
|---|---|---|
| **Nature of effect** | **Severity** *(mild, moderate, severe)* | **Frequency** *(very rare, rare, probable, frequent)* |
| • **Peri-implant mucositis** | | |
| Bleeding (BOP Bleeding On Probing) | mild | probable |
| Bruising | mild | frequent |
| Delayed healing of the gum | mild | rare |
| Inflammatory papillary hyperplasia | mild | probable |
| Gingival/mucosal hyperplasia | mild | probable |
| Pain | mild to moderate | probable |
| Recession/dehiscence of the gum | moderate | rare |
| Redness | mild | probable |
| Suppuration | moderate | probable |
| Swelling/gingival inflammation | mild | probable |
| • **Peri-implantitis** | | |
| Bleeding (BOP Bleeding On Probing) | mild | probable |
| Bone loss around implant | moderate | probable |
| Bruising | mild | frequent |
| Infection at implant site without suppuration (not recurrent) | mild to moderate | probable |
| Infection at implant site with suppuration (not recurrent) | moderate | rare |
| Recurrent infection at implant site without suppuration | moderate to severe | rare |

| | | |
|---|---|---|
| Recurrent infection at implant site with suppuration | moderate to severe | rare |
| Systemic infection | severe | very rare |
| Pain | mild to moderate | probable |
| Swelling | mild | probable |
| • **Bone integration deficiency** | | |
| Early loss/exfoliation (within 2 weeks after surgery) | moderate | probable |
| Late loss/exfoliation (after prosthetic restoration) | moderate | probable |
| No primary stability (at surgery) | moderate | rare to probable |
| Implant mobility (tactile horizontal or vertical) | moderate | rare to probable |
| Radiolucency | mild to moderate | probable |
| Aspiration of implant | severe | very rare |
| Swallowing of implant | severe | very rare |
| • **Non-plaque related** | | |
| Chronic pain in connection with the dental implant | mild to moderate | rare |
| Foreign body sensation | mild | probable |
| Material allergy | moderate | rare |
| Oro-sinus or oro-nasal intrusion/fistula | severe | very rare |
| Permanent paresthesia, dysesthesia | severe | rare |
| Temporary or permanent nerve damage in the jaw | severe | very rare |
| **Mechanical complications** | | |
| **Nature of effect** | **Severity** *(mild, moderate, severe)* | **Frequency** *(very rare, rare, probable, frequent)* |
| Loosening of abutment screw | mild | probable |
| Loosening of an healing cap | mild | probable |
| Loosening of prosthetic screw | mild | probable |
| Lost/failure of an abutment | moderate | probable |
| Lost/failure of an healing cap | mild | probable |
| Fracture of abutment screw | moderate | probable |

| | | |
|---|---|---|
| Fracture of prosthetic screw | mild | probable |
| Fracture of implant | moderate | rare |
| **Technical complications** | | |
| **Nature of effect** | **Severity** *(mild, moderate, severe)* | **Frequency** *(very rare, rare, probable, frequent)* |
| Failure of prosthesis (framework, opposing framework) | moderate | rare |
| Fracture of prosthesis | mild to moderate | probable |
| Fracture of veneering material | mild | probable |
| Irreversible damage to adjacent/opposing teeth | moderate | rare |
| Loss of cement retention of prosthesis | mild | probable |
| **Other complications** | | |
| **Nature of effect** | **Severity** *(mild, moderate, severe)* | **Frequency** *(very rare, rare, probable, frequent)* |
| Aesthetic problem | mild | rare |
| Aspiration of component(s) (other than implant) | severe | very rare |
| Jaw, bone fracture | moderate to severe | very rare |
| Phonetic difficulties | mild to moderate | rare |
| Swallowing of component(s) (other than implant) | severe | very rare |
| Hypersensitivity (adjacent teeth) | mild | probable |

## 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/SAE case 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 AE, data should be entered into the AE case report form in the EDC system within five working days of awareness of the event. Safety reporting to the 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 case report form should be completed in the EDC within 24 hours of awareness of the event. Straumann will receive an automated notification generated by the EDC system.

Safety reporting to the 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 by completing the Device Deficiency CRF.

When a device deficiency leads to a potential AE (e.g. bleeding, pain, swelling, infection, peri-implantitis) the AE case report form in the database needs to be completed in a timely manner.

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

### 7.3.4 ADE Reporting

Adverse device effects must be recorded and submitted to Straumann by completing the AE case report form in the EDC system within five working days of awareness of the event. Safety reporting to the Institutional Review Board (IRB) should occur according to the requirements of the local IRB.

Bone loss reporting: Continuous substantial reduction of the peri-implant bone level is a sign of failure of the implant system. The first European Workshop on Periodontology specified an average marginal bone loss of less than 1.5 mm bone loss within the first year after the insertion of the prosthesis, and thereafter less than 0.2 mm annual bone loss as criteria for measuring success[18]. This has been a standard and a basis for success criteria since it was defined in 1993. In a more recent meta-analysis, the authors looked at Straumann implants and determined that a pooled weighted mean of marginal bone level change for Straumann implants was -0.56 mm (95% CI -0.661, -.481) after 5 years. The individual study means of marginal bone level change ranged from -0.15 to -1.0 mm after 5 years.[19] Based on this information the central radiologist will flag any bone level changes that are greater than 2.5 mm in the first year post-loading and any annual changes greater than 1.5 mm in subsequent years. The study manager will review the flagged values and discuss with the principal investigator whether the bone level change will be reported as an ADE.

### 7.3.5 SADE Reporting

In the occurrence of a serious adverse device effect, expedited reporting requirements are followed. The SAE case report form should be completed within 24 hours of awareness of the event in the EDC system. Straumann will receive an automated notification generated by the EDC system.

The product safety officer at Straumann will work with the Investigator to determine whether the event is anticipated (ASADE) or unanticipated (USADE). In case of USADE, the investigator must promptly notify its reviewing IRB as soon as possible, but no later than ten (10) working days after first learning of the event.

Since this is a multi-center study, Straumann will inform investigators at all participating centers of any reported USADEs related to this protocol and the study device. Copies of such external USADE reports should be forwarded to the IRB for review and a copy must be kept in the investigator site files.

### 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.

The outcome of an event will be pursued until resolution or until the last data queries are issued following the subject's last study visit. For screen failure subjects, ongoing AEs, ADEs, and DDs must be followed and updated until the date the subject is deemed a screen failure. For subjects documented as lost to follow-up, ongoing AEs, ADEs, and DDs will not be followed.

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 Considerations

### 8.1 Sample Size

The following assumptions were used to determine the sample size for the primary endpoint of mean change in crestal bone level between implant placement and 12 months post-implant loading:

- Subjects will be assigned to either the test or control treatment group
- The primary analysis is a non-inferiority comparison of the test treatment to the control treatment

- The standard deviation for both test and control treatments is 0.5 mm
- A difference between treatment groups of ≥ 0.5 mm is considered clinically significant (i.e., the non-inferiority margin)
- The difference between the treatment groups is expected to be 0 mm
- Greater than 80% power is considered sufficient
- Statistical test will be performed with a one-sided 5% significance level

The hypotheses associated with the primary endpoint are defined as follows:

$$H_0: \mu_c \geq \mu_s + \delta$$

$$H_1: \mu_c < \mu_s + \delta$$

where $\mu_c$ is the mean change in crestal bone level for the test implants, $\mu_s$ is the mean change in crestal bone level for control implants, and $\delta$ is the pre-defined non-inferiority margin of 0.5 mm. The study will be considered successful if the null hypothesis is rejected, i.e., the conclusion of non-inferiority is achieved. If non-inferiority is achieved at a one-sided $\alpha$ of 5%, a one-side superiority test will be performed at significance level of 5%.

To maintain at least 80% power to detect a difference between treatment groups of 0.5 mm with a common standard deviation of 0.5 mm, 14 subjects per treatment group would be required for a total of 28 subjects. Adjusting for potential 25% attrition, 19 subjects per treatment group will be required for a total of 38 subjects. An additional 14 subjects will be enrolled in order to provide more data for the implant success and survival calculations, thereby bringing the total sample size to 52.

## 8.2 Randomization

The randomization schedule will be generated and held by an independent statistician that will not participate in any other aspect of the study. Subjects will be randomized to either test or control in a 1:1 ratio.

The study randomization schedule will be stratified by study center to ensure that randomization is balanced across the two centers. Further, the randomization will use permuted blocks of appropriate size.

## 8.3 Analysis Sets

### 8.3.1 Modified Intention to Treat (mITT) Analysis Set

The analysis of the primary and secondary effectiveness measures will be based on the mITT analysis set. The modified intent to treat analysis set consists of all subjects who are consented in the study, randomized, and received the study device. This analysis set will include subjects regardless of any protocol violations and/or premature termination. This analysis set includes the Per Protocol analysis set.

### 8.3.2 Intention to Treat (ITT) Analysis Set

The ITT analysis set consists of all subjects who are consented in the study, and randomized (i.e., enrolled). This population will include subjects regardless of any protocol violations and/or premature termination, or whether the subject actually received study treatment, and is based on the subject's randomization assignment rather than actual treatment received. The ITT analysis set will be used for presenting baseline data, procedural information, adverse events and protocol deviations. The ITT analysis set will also be used to provide a sensitivity analysis of the primary effectiveness endpoint. This analysis set includes the mITT population.

### 8.3.3 Per Protocol (PP) Analysis Set

The PP analysis set consists of all subjects who are consented in the study, randomized, and received the study device according to the study protocol and randomization schedule. Subjects with significant protocol deviations (e.g., deviation of inclusion/exclusion criteria) will be excluded from this analysis set. Subjects with implants that do not reach primary stability will be excluded from this analysis set. Exclusion of subjects based on protocol deviations will be determined on a case-by-case basis with input from the Principle Investigator and study statistician. The determination of which protocol deviations are significant enough to warrant exclusion from PP analysis population will be made while blinded to the subject's randomization assignment and primary endpoint result, and prior to final analysis. The PP analysis set will be used to provide a sensitivity analysis of the primary effectiveness endpoint.

The results based on the ITT and PP analysis sets are intended only to assess the robustness of the primary findings based on the mITT population.

## 8.4 Effectiveness Analysis Methods

### 8.4.1 Analysis of Primary Endpoint

Change in crestal bone level between implant loading and 12 months post-loading will be measured as the primary endpoint. Crestal bone levels on both the mesial and distal aspect of the implant will be considered and the mean of the two measurements will be used as the primary endpoint. If only one of the two measurements is available, the available measurement will be used in the analysis. The hypothesis tested is described in Section 8.1.

Mean change in crestal bone level between treatment groups will be compared via a one-sided t-test. If assumptions of normality are violated, an appropriate non-parametric method or data transformation will be sought.

Additional summaries with subjects categorized into one of the following groups based on the change in crestal bone level: bone gain, no change, 0 to <1 mm loss, 1 mm to <2 mm loss, 2 mm to <3 mm loss, and ≥3 mm loss will be presented.

Summary statistics of the primary endpoint will be presented for raw values and change from baseline overall and by study center. If it is believed that the primary endpoint results may be affected by study center, ANCOVA methods may be used with treatment assignment as main effect and study center as a covariate. Other covariates, including implant site, implant length, racial data, age, gender, history of tobacco use, controlled diabetes, full-mouth plaque score, simultaneous grafting may also be added as covariates in the exploratory analyses.

### 8.4.2 Analysis of Secondary Endpoints

All secondary effectiveness endpoints will be summarized descriptively and no hypothesis tests are planned. Secondary endpoints include implant success and survival rates, implant stability as measured by RFA, dimensional changes of the buccal bone as measured on CBCT images, changes in soft tissue measurements (gingival and papilla margins – baseline at final restoration), and subject satisfaction (esthetics, function, and level of pain).

### 8.4.3 Analysis of Additional Endpoints

Additional effectiveness measures will be collected at 24-, 36-, 48-, and 60-months post implant loading. These endpoints will be summarized descriptively and no hypothesis testing is planned. The additional endpoints include implant success and survival rates, dimensional changes of the buccal bone as measured on CBCT images, changes in soft tissue measurements (gingival and papilla margins – baseline at final restoration), and subject satisfaction (esthetics, function, and level of pain)..

### 8.4.4 Analysis of Safety Endpoints

For analysis of safety endpoints, summary tables and/or listings will be provided for all adverse events by event category. Adverse events will also be summarized by relationship to the study device, implant procedure, by seriousness, severity and by outcome. Adverse events leading to discontinuation from the study will be tabulated. Except where indicated, a subject reporting the same adverse event more than once will be counted once when calculating the number and percentage of subjects with that particular event. Except where indicated, if a subject reports the same adverse event more than once, the strongest relationship to the procedure and/or device recorded for the event will be presented.

Adverse events that occurred in screen failure subjects will be presented separately.

## 8.5 General Statistical Methods

A qualified statistician using validated statistical software will perform all statistical analyses. Unless otherwise specified, the data will be summarized for non-missing subjects in tables listing the mean, standard deviation, minimum, maximum, and number of subjects in a group of continuous data, or number of subjects and percentage in each category for categorical data, as appropriate. In general the denominator for the percentage calculation will be based upon the total number of subjects (N) in the study population for the treatment groups, unless otherwise specified.

All the statistical tests will be based on a 2-sided test at the significance level of 0.05, unless otherwise specified.

### 8.5.1 Balance in Baseline Characteristics

To assess balance in baseline characteristics, the distribution of each baseline variable of interest will be compared between the two treatment groups. 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).

All baseline demographic variables and other characteristics (including history of tobacco use, oral situation (number of missing teeth, natural teeth and number of implants), reason for tooth extraction/loss, modified sulcus bleeding index, pocket probing depths at 6 sites on adjacent teeth, and oral hygiene) will be summarized by treatment group.

### 8.5.2 Surgery and Supporting Procedures

Summaries of select surgery and other supportive measures will be presented by treatment group.

Detailed information regarding the surgical procedure will be presented in listings. This will include information on crestal bone measurements, bone quality, evaluation of primary stability, guided bone regeneration, and soft tissue procedures.

Details regarding other supportive procedures in the study will be presented in listings, including suture removal, second stage surgery, soft tissue procedures, impressions, temporary prosthesis placement, and final prosthesis placement.

### 8.5.3 Other Data Summaries

Concomitant medications will be presented in listings and also summarized by drug category. Protocol deviations will be summarized by deviation type and study center.

### 8.5.4 Subject Disposition

A detailed description of subject disposition will be provided by study group using a CONSORT diagram and summaries of subjects falling in various subgroups of interest,

such as enrolled but did not receive study treatment and early withdrawals. All enrolled (i.e., randomized) subjects entered in the study will be accounted for in the summary.

### 8.5.5 Missing Data

Every effort will be made to minimize the amount of missing data. If a subject drops 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.

The primary effectiveness measure of change in crestal bone level will be based on available data. Sensitivity analyses based on last observation carried forward will be performed if missing data of the primary endpoint exceeds 10%. Other techniques for sensitivity may be explored.

If standard statistical tests or clinical review indicate the presence of outliers for the primary endpoint, an additional analysis excluding such outliers will also be performed and the rationale for such exclusion will be described completely.

## 9 Data Management

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

Required clinical data for this study will be collected and recorded in the clinical database using an electronic case report form 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 electronic signature of all electronic case report forms. The information entered into the database will be checked systematically by the data management for inconsistent, illogical and/or missing data using electronic and manual validation checks defined in the Data Validation Plan. If validation of data leads to discrepancies, data management will generate electronic 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 data system used for this study has a security system that prevents unauthorized access to the data and any deletion of data (audit and edit trail).

# 10 Study Management

## 10.1 Regulatory and Ethical Requirements

### 10.1.1 Informed Consent

Informed consent will be obtained from all subjects prior to study participation as described in Section 4.1.1.

### 10.1.2 Institutional Review Board

Prior to initiation of any study procedures, the protocol and informed consent will be submitted to an 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 sponsor must receive a letter documenting the IRB approval at the center prior to the initiation of the study at the center.

The investigator is responsible for providing the appropriate reports to the IRB during the course of the clinical study. This will include 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

## 10.2 Reports and Record Management

### 10.2.1 Investigator Records

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
- IRB approval letter and IRB approved informed consent document

### 10.2.2 Case Report Forms

The investigator will be responsible for the accuracy of the data entered on the Electronic Case Report Forms (eCRFs). The investigator will also allow a Straumann representative and/or regulatory bodies to review the data reported on the case report form with the source documents as far as is permitted by local regulations.

### 10.2.3 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. All source documents pertaining to this study will be maintained by the investigator and made available for inspection by authorized persons.

### 10.2.4 Records/Data Retention

Original radiographs, photographs, and study documents will be maintained at the research center in a file established for this study. All study documentation needs to be stored at the research center for at least fifteen (15) 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 standard operating procedures.

## 10.3 Monitoring

Straumann will assign a qualified individual to monitor the study. The general monitoring procedures for this study are described below, details can be found in the Monitoring Plan.

### 10.3.1 Study Initiation Visit

Once a site receives IRB approval, 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

### 10.3.2 Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically, 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 will allow Straumann to have access to all study documents during each monitoring visit for a thorough review of the study's progress.

### 10.3.3 Study Closeout Visit

After the last subject has completed the study and the database has been cleaned, the closeout visit will be conducted at the center. The following tasks should be completed by Straumann or the monitor:

- Review any outstanding questions from the Clinical Investigation Report and organize the signature process
- Ensure that the documentation and clinical investigation requirements were met
- Collect outstanding documents

- Ensure that adverse events were reported to the IRB according to the IRB's policy
- Ensure that device accountability is complete
- Organize the archiving of all study-related documents and remind the investigator of the obligation to retain the records

## 10.4 Study Termination

At study termination, a Clinical Investigation Report will be prepared by the sponsor, even if the study was terminated prematurely.

The study can be terminated early 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

### 10.4.1 Center 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 effect the integrity of the study or the study data

## 10.5 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.

## 10.6 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.

## 11 Protocol Signature Page

Protocol: CR 01/14

Study Title: Immediate Placement of the Straumann® Bone Level Tapered Implant with Early Loading in Single Tooth Gaps in the Maxilla and Mandible Compared to Delayed Placement

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 Principal Investigator | Signature of Principal Investigator | Date |

**Received by Sponsor:**

| Printed Name of Study Manager | Signature of Study Manager | Date |
|---|---|---|

## 12 References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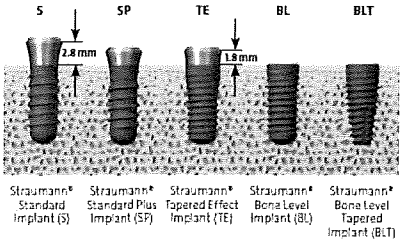
# Appendix 1 – Instructions for Use

straumann
simply doing more





| | | |
|---|---|---|
| English | Instructions for use: Straumann® Dental Implants: Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level and Bone Level Tapered | 2–4 |
| Deutsch | Gebrauchsanweisung: Straumann® Zahnimplantate: Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level und Bone Level Tapered | 5–7 |
| Français | Mode d'emploi : Implants dentaires Straumann® : Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level et Bone Level Tapered | 8–10 |
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| Español | Instrucciones de uso: Implantes dentales Straumann®: Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level y Bone Level Tapered | 14–16 |
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Manufacturer / Hersteller / Fabricant /
Produttore / Fabricante / Fabricante

Institut Straumann AG, Peter Merian-Weg 12
CH-4002 Basel/Switzerland, www.straumann.com



Version (RD-RR-RT/max.): 07 / 07

**English**

# Instructions for use: Straumann® Dental Implants: Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level and Bone Level Tapered

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

## Product Description

The Straumann® Dental Implant System is an integrated system of endosseous dental implants with corresponding abutments, healing abutments, closure screws and surgical and prosthetic parts and instruments.

Straumann® Roxolid® Dental implants are solid screw implants comprised of a titanium-zirconium alloy with a SLActive® bone anchorage surface that is large-grit sandblasted and acid-etched. In addition, SLActive® is in a chemically activated state, which is preserved by storage in a NaCl solution. After removal from its liquid filled packaging, the properties of the SLActive® surface are preserved for at least 15 minutes. The implant should be inserted within this period.
Straumann® Dental implants used for guided surgery are specifically adapted with respect to the transfer piece. This allows for guided implant insertion through the surgical template.

## Intended use

The Straumann® Dental Implants are suitable for the treatment of oral endosteal implantation in the upper and lower jaw and for the functional and esthetic oral rehabilitation of edentulous and partially dentate patients. Straumann® Dental implants can be used for immediate or early implantation following extraction or loss of natural teeth. Implants can be placed with immediate function on single-tooth and/or multiple-tooth applications when good primary stability is achieved and with appropriate occlusal loading, to restore chewing function. The prosthetic restorations used are single crowns, bridges and partial or full dentures, which are connected to the implants by the corresponding elements (abutments).

The guided implants (implant with guided transfer pieces) shall give the possibility to the customer to insert an implant in a guided manner through a surgical template.

## Indications

Straumann® Dental implants are suitable for the treatment of oral endosteal implantation in the upper and lower jaw and for the functional and aesthetic oral rehabilitation of edentulous and partially dentate patients. Straumann® Dental implants can also be used for immediate or early implantation following extraction or loss of natural teeth. Implants can be placed with immediate function on single-tooth and/or multiple-tooth applications when good primary stability is achieved and with appropriate occlusal loading to restore chewing function. The prosthetic restorations used are single crowns, bridges and partial or full dentures, which are connected to the implants through the corresponding components (abutments).

## Contraindications

Inadequate bone volume and/or quality, local root remnants, serious internal medical problems, uncontrolled bleeding disorders, inadequate wound healing capacity, not completed maxillary and mandibular growth, poor general state of health, uncooperative, unmotivated patient, drug or alcohol abuse, psychoses, prolonged therapy-resistant functional disorders, xerostomia, weakened immune system, illnesses requiring periodic use of steroids, uncontrollable endocrine disorders. Allergies or hypersensitivity to chemical ingredients of materials used: titanium-zirconium alloy.

## Side effects, interactions and precautions; complications with Straumann implants

Information related to side effects, interactions and precautions; complications with Straumann implants should be provided to the patient.
Immediately after the insertion of dental implants, activities that demand considerable physical exertion should be avoided. Possible complications following the insertion of dental implants are:

### Temporary symptoms

Pain, swelling, phonetic difficulties, gingival inflammation

### More persistent symptoms

Chronic pain in connection with the dental implant, permanent paresthesia, dysesthesia, loss of maxillary/mandibular ridge bone, localized or systemic infection, oroantral or oronasal fistulae, unfavorably affected adjacent teeth, irreversible damage to adjacent teeth, fractures of implant, jaw, bone or prosthesis, aesthetic problems, nerve damage, exfoliation, hyperplasia

## Warning

- Products must be secured against aspiration when handled intraorally. Aspiration of products may lead to infection or unplanned physical injury.
- Avoid approaching the proximity of the mandibular nerve channel during implant bed preparation and implant insertion. Nerve damage may result in anesthesia, paresthesia and dysthesia.

## Cautions/Precautions

- Always select the largest diameter implant that can be supported by the available bone thickness, bone quality, inter-dental spacing, and anticipated mastication forces. Particular care should be taken to assure proper implant alignment where comparatively high loads are expected. Small-diameter implants are not recommended for the posterior region.
- A careful clinical and radiological examination of the patient should be performed prior to surgery to determine the psychological and physical status of the patient. Special attention should be given to patients who have local or systemic factors that could interfere with the healing process of either bone or soft tissue or the osseointegration process (e.g. bone metabolism disturbances, previously irradiated bone in the head or neck area, diabetes mellitus, anticoagulation drugs/hemorrhagic diatheses, bruxism, parafunctional habits, unfavorable anatomic bone conditions, tobacco abuse, untreated periodontal diseases, acute infection of implant site, temporomandibular joint disorders, treatable pathologic diseases of the jaw and changes in the oral mucosa, pregnancy, inadequate oral hygiene).
- Sterile handling is essential. Never use potentially contaminated components. Contamination may lead to infections.
- The implants must be stored in a dry place in the original packaging, protected from direct sunlight and at room temperature. Improper storage may compromise essential material and design characteristics leading to device failure.
- Do not re-sterilize Straumann® Dental implants. Cleaning, disinfection and sterilization may compromise essential material and design characteristics leading to device failure.
- Do not re-use Straumann® Dental implants. Re-use of single-use devices creates a potential risk of patient or user infections.
- Avoid corrections of the vertical position using reverse rotations (counterclockwise). This can cause loosening of the screw-retained transfer piece and may lead to a decreased primary stability.
- For Guided Surgery please make sure to use the stop key with the flat side pointing towards the sleeve, otherwise the implant cannot be inserted to the final insertion depth.

- The Straumann® Dental implants have not been evaluated for safety and compatibility in the Magnetic Resonance environment. The Straumann® Dental implants have not been tested for heating or migration in the Magnetic Resonance environment.
- Because of the reduced surface area for anchorage in the bone, implants with 6 mm length should be used for the following indications only: as an additional implant together with longer implants to support implant-borne reconstructions or as an auxiliary implant for implant-borne bar constructions supporting full dentures in a seriously atrophied mandible.

## Compatibility information

Straumann® Dental implants and the prosthetic lines synOcta®, CrossFit® and Narrow Neck CrossFit® are available in a variety of configurations. Make sure that you use only Straumann® parts with the corresponding connection for the restoring of a Straumann® Dental implant (e.g. for prosthetic platform RN (Regular Neck) only components marked with RN can be used). For further information see brochures "Basic Information" as mentioned in "Further Information".
Only Straumann® Dental implants labelled with 'Guided Surgery' are suitable for insertion through Straumann® Guided Surgery templates. For additional information see "Basic Information on Straumann® Guided Surgery – Straumann® Dental Implant System".

| Implant type | Connection type | Compatible parts |
|---|---|---|
| BL (Bone Level) | NC (Narrow CrossFit®) Ø 3.3 mm | parts labeled NC |
| | RC (Regular CrossFit®) Ø 4.1/4.8 mm | parts labeled RC |
| BLT (Bone Level Tapered) | NC (Narrow CrossFit®) Ø 3.3 mm | parts labeled NC |
| | RC (Regular CrossFit®) Ø 4.1/4.8 mm | parts labeled RC |
| S (Standard) SP (Standard Plus) TE (Tapered Effect) | NNC (Narrow Neck CrossFit® Ø 3.5 mm | parts labeled NNC |
| | RN (Regular Neck) Ø 4.8 mm | parts labeled RN |
| | WN (Wide Neck) Ø 6.5 mm | parts labeled WN |

## Cleaning and disinfection

Straumann® Dental implants are provided sterile and for single use only. They must not be cleaned and sterilized. **Institut Straumann AG does not accept any responsibility for re-sterilized implants, regardless of who has carried out re-sterilization or by what method.**

## Sterilization

Straumann® Dental implants are delivered sterile. The intact sterile packaging protects the sterilized implant from outside influences and, if stored correctly, ensures sterility up to the expiration date. When removing the implant from the sterile packaging, rules of asepsis must be observed. The sterile packaging must not be opened until immediately prior to insertion of the implant. Implants with damaged sterile packaging must not be used. It is recommended to have a replacement implant on hand.
**Institut Straumann does not accept any responsibility for re-sterilized implants, regardless of who has carried out re-sterilization or by what method. A previously used or non-sterile implant must not be implanted under any circumstances. If the original packaging is damaged, the contents will not be accepted back by Institut Straumann.**

## Procedure

Consult the brochures "Basic Information" as mentioned in "Further Information" for a detailed step-by-step description.

### Preoperative planning

The implant diameter, implant type, position and number of implants should be selected individually taking the anatomy and spatial circumstances into account. The specific measurements should be regarded as minimum guidelines and are further specified in the "Basic Information on the Surgical Techniques".

### Implant bed preparation

Thermal trauma prevents healing of a dental implant. Excessive rises in temperature must therefore be minimized by following the "Guidelines for the use of Straumann® Dental Implant System drills and instruments" regarding rotations per minute, intermittent drilling techniques and adequate cooling.

### Insertion of the implant

A Straumann® Implant can be placed either manually with the ratchet or with the aid of thehandpiece. A maximum speed of 15 rpm is recommended.

### Treatment of soft tissue, wound closure

Prior to wound closure, the appropriate closure screw or healing cap is selected and screwed on to the implant. Consult the corresponding package insert when using healing caps and closure screws.

## Healing phase

Straumann® Dental implants are suitable, within the scope of indications, for immediate and early restoration in single-tooth gaps and in an edentulous or partially edentulous jaw. Good primary stability and an appropriate occlusal load are essential.
In case of immediate restoration: In partially edentulous jaws two or more adjacent implants should be prosthetically connected together. In edentulous jaws at least 4 implants must be connected together. For minimal healing time for relevant Straumann® Dental implants refer to the "Basic Information on the Surgical Procedures".
Radiographic check is recommended after a healing phase before starting the prosthetic restoration.

## Further information

You will find further information regarding treatment recommendation and use of different types of Straumann® Dental implants and other components of the Straumann® Dental Implant System in the documentation that is available on request from Straumann. Ensure that the following brochures, in particular the surgical brochures, are available.

Brochures:
- "Basic Information on the Surgical Procedures – Straumann® Dental Implant System"
- "Basic Information on the Surgical Procedures - Straumann® Bone Level Tapered Implants"
- "Basic Information on Straumann® Guided Surgery – Straumann® Dental Implant System"
- "Care and Maintenance of Surgical and Prosthetic Instruments"

Package inserts:
- "Guidelines for the use of Straumann® Dental Implant System drills and instruments"
- "Instructions for the use of Straumann® Dental Implant System closure screws, healing caps and healing abutments"

## Please note

Practitioners must have knowledge of dental implantology 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.

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.

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



**Availability**
Some items of the Straumann® Dental Implant System are not available in all countries.

CE 0123 Straumann Products with the CE mark fulfill the requirements of the Medical Devices Directive 93/42 EEC


Consult instructions for use
Please follow the link to the e-IFU
www.ifu.straumann.com


Do not re-use

Batch code


Use before expiry date

Article number


Manufacturer


Keep away from sunlight


Sterilized using irradiation

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



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## Appendix 2 – 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 fulfilment 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.

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.

## Appendix 3 – Visual Analog Scale

| straumann<br>CR 01/14 | Subject Initials: | | Visit 9<br>12 Month Follow-Up |
|---|---|---|---|
| | Subject ID: | - | |
| | Date: | / / | |

**To be completed by the patient - comment on the implant and supported crown**

**Pain associated with the implant and crown**

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

Painful _____ No pain

**Satisfaction with the function**

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

Not Satisfied _____ Highly Satisfied

**Satisfaction with the esthetics**

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

Not Satisfied _____ Highly Satisfied

Patient's Signature: _____ Date: / /