A randomized controlled study to assess intra-patient clinical performance of dental implants with a SLActive® vs. SLA® surface

CR 2017-05

Date: 26 Feb 2020

Version 3.0

Protocol reviewed and approved by:

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Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BoP	Bleeding on Probing
ECRF	Electronic Case Report Form
DD	Device Deficiency
EC	Ethics Committee
EDC	Electronic Data Capturing
FMPS	Full Mouth Plaque Score
GCF	Gingival Crevicular Fluid
GCP	Good Clinical Practice
IfU	Instructions for Use
ISO	International Organization for Standardization
ISQ	Implant Stability Quotient
ITI	International Team for Implantology
MBL	Marginal Bone Loss
OHRQoL	Oral Health Related Quality of Life
OHIP	Oral Health Impact Profile
PPD	Probing Pocket Depth
RFA	resonance frequency analysis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

SLA® Sandblasted, large-grit, acid-etched (surface)

SLActive® Chemically modified SLA® (surface)

UFS Ultra-fine structure

USADE Unanticipated Serious Adverse Device Effect

Synopsis

Study Title	A randomized controlled study to assess intra-patient clinical performance of dental implants with a SLActive® vs. SLA® surface
Study Protocol Number	CR 2017-05
Study Registration	clinicaltrials.gov (NCT03737357)
Objectives	• to confirm safety and clinical performance of SLActive® implants • to evaluate the osseointegration and anti-inflammatory potential of the SLActive® surface compared to SLA®.
Hypotheses	Co-primary study hypotheses: • SLActive® implants are safe • 12 months after loading, the marginal bone loss around the SLActive® implants will not be appreciably greater than around the SLA® implants. Secondary study hypotheses: • SLActive® implants show superior osseointegration compared to SLA® as tested by biomarker analysis • SLActive® implants show superior anti-inflammation compared to SLA® as tested by biomarker analysis
Design	Prospective, single-blinded, randomized, paired sample, multi-center clinical study
Study Population	Male or female subjects over 18 years of age and in need of two or more dental implants (canine to molars) placed in two different quadrants.
Patient Inclusion Criteria	The following criteria must be met for inclusion in the study: • Males and females, at least 18 years old • Partially edentulous patients in need of two or more dental implants (canine to molars) placed in two different quadrants in healed sites (3 months post extraction) • Subject must have voluntarily signed the informed consent, is willing and able to attend scheduled follow-up visits, and agrees that the encoded data will be collected and analyzed
Patient Exclusion Criteria	The following exclusion criteria will lead to exclusion from the study: • Any contraindications for oral surgical procedures • Dental implant placement contraindicated according to Instructions for Use (IFU) • Subjects with inadequate oral hygiene (FMPS ≥ 20%) • Subjects who are currently heavy smokers (defined >10 cigarettes per day or >1 cigar per day) or who use chewing tobacco. • Subjects with drug or alcohol abuse • Patients requiring soft tissue and bone grafting procedures • Patients having had soft tissue grafting procedures within the last 3 months and bone grafting procedures within the last 6 months in the region where a study implant is planned • Keratinized soft tissue height of less than 2 mm where a study implant is planned • Inadequate bone volume • Severe bruxism or clenching habits • Women who are pregnant or planning to become pregnant at any point during the study duration. • patients who have systemic factors that could interfere with the healing process of either bone or soft tissue or the osseointegration process (e.g. bone metabolism disturbances,

<table>
<tr><td></td><td colspan="3">uncontrolled diabetes mellitus, anticoagulation drugs/ hemorrhagic diatheses)
• patients with local factors that could interfere with the healing process, such as untreated periodontal diseases, acute infection of implant site, temporomandibular joint disorders, treatable pathologic diseases of the jaw and changes in the oral mucosa)
• 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>Study Treatment</td><td colspan="3">One study test (SLActive® surface) and one study control (SLA® surface) implant (Bone Level Tapered, Roxolid®) will be placed in two different quadrants of partially edentulous patients. The implants will be placed at premolars, molars and canine positions in the mandible and maxilla (healed extraction sites). Implants will be restored with a single crown or splinted restorations 10 weeks after implant placement.</td></tr>
<tr><td rowspan="10">Treatment Plan</td><td>Visit #</td><td>Visit</td><td>Schedule</td></tr>
<tr><td>Visit 1</td><td>Screening</td><td>Up to 10 weeks before implant placement</td></tr>
<tr><td>Visit 2</td><td>Implant placement and sampling (baseline)</td><td>Day 0</td></tr>
<tr><td>Visit 3</td><td>Sampling, suture removal</td><td>1 week (+/-1 days)</td></tr>
<tr><td>Visit 4</td><td>Sampling</td><td>2 weeks (+/-2 days)</td></tr>
<tr><td>Visit 5</td><td>Sampling</td><td>4 weeks (+/-3 days)</td></tr>
<tr><td>Visit 6</td><td>Sampling, final impression</td><td>8 weeks (+/-5 days)</td></tr>
<tr><td>Visit 7</td><td>Implant loading</td><td>10 weeks (+/- 10 days)</td></tr>
<tr><td>Visit 8</td><td>6-month FU</td><td>6 months (+/-2 week) after loading</td></tr>
<tr><td>Visit 9</td><td>12-month FU</td><td>12 months (+/-3 weeks) after loading</td></tr>
<tr><td>Test Device</td><td colspan="3">Bone Level Tapered (BLT) Roxolid® implants with a SLActive® surface (8, 10, 12 or 14 mm length and 3.3 or 4.1 mm diameter).</td></tr>
<tr><td>Control Device</td><td colspan="3">Bone Level Tapered (BLT) Roxolid® implants with a SLA® (surface 8, 10, 12 or 14 mm length and 3.3 or 4.1mm diameter).</td></tr>
<tr><td>Registration Status</td><td colspan="3">All products are CE marked and used within their intended purpose</td></tr>
<tr><td>Analysis</td><td colspan="3">The final analysis will be conducted after all patients completed the 12-month visit. Optional interim analysis will be performed after all patients completed the completion the 8 weeks follow-up visit.</td></tr>
<tr><td>Primary Endpoints</td><td colspan="3">- Bone level change at 12 months after implant loading.
- Occurrence of adverse device effects and device deficiencies that could have led to a serious adverse device effect</td></tr>
<tr><td>Secondary Endpoints
.</td><td colspan="3">- Bone level change (between implant placement and loading and between loading and 12 months after implant loading).
- Changes of biomarkers in GCF in regards to:
- Inflammation (between implant placement and 30 days):</td></tr>
</table>

	Anti-inflammatory biomarkers analysis (concentrations of IL-10 and IL-4) Inflammatory biomarkers (concentrations of IL-6, IL-1 β TNF-α, IL-2) - Osseointegration (between day 7 and 8 weeks): concentrations of VEGF Osteocalcin (OCN), osteopontin (OPN) - Bacterial load analysis (between implant placement and 30 days) - Implant stability (with ISQ) (between implant placement and 8 weeks) - Soft tissue/ wound healing (Landry index) (between suture removal and 14 days) - Clinical measurements Keratinized tissue height at implant placement and after 12 months. Probing pocket depth (PPD) and Bleeding on Probing (BoP) after 12 months FMPS (at screening and after 12 months) - Implant survival (up to 12 months) - Prosthetic success (prosthetic survival and prosthetic complications) (up to 12 months) - Patient satisfaction (OHRQoL, OHIP-14 questionnaire) (at screening, loading and after 12 months)
Safety	The patients will be monitored for AEs and device deficiencies by the Investigators.
Participating Countries	Spain
Number of participating centers	2 (one university hospital in Madrid and one university hospital in Santiago de Compostela)
Number of Patients planned to be enrolled	60
Study Duration	Approximately 26 months in total. Study started in October 2019, end of the study planned in November 2021
Follow-up period	12 months from loading (loading after 10 weeks)
Sponsor	Institut Straumann AG
Investigators	Prof. Dr Mariano Sanz, Universidad Complutense (Complutense University), Facultad de Odontologia, Plaza Ramon y Cajal s/n, 28040 Madrid, Spain (Coordinating Investigator) Prof. Dr Juan Blanco, Universidad de Santiago de Compostela, Facultad de Medicina y odontología, Departamento de Cirugía y Especialidades médico-quirúrgicas (Odontología), Unidad de Periodoncia, C/ Entrerrios s/n, 15782 Santiago de Compostela, Spain
Compliance	This study and any amendments will be performed according to International Organization for Standardization (ISO) 14155:2011 as far as applicable for post-market studies, local legal and regulatory requirements, and conform to the Declaration of Helsinki (last revision Fortaleza 2013).

Table of Content

1 Background and Study Rationale

Restoring missing teeth with dental implants is becoming a mainstream treatment option and patients expect successful and predictable treatment results. The clinical success of oral implants depends on the interaction with surrounding bone ultimately resulting in osseointegration. An important role thereby plays the implant surface (1) (2). SLActive® (Chemically modified Sandblasted, large-grit, acid-etched) is a hydrophilic, chemically active implant surface with ultra-fine structures. The surface has been investigated in various pre-clinical and clinical studies and the results showed high predictability and accelerated osseointegration (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) compared to hydrophobic surfaces.

Straumann has optimized the production process of Straumann® SLActive® implants to better control the SLActive® surface properties. Under normal storage conditions – storage in an aqueous saline solution at a room temperature (for details see the surface research document PDD-00017370 (13)), SLActive® implants spontaneously develop ultra-fine structures (UFS) within 2 to 6 months. Now, a postproduction-holding step at 55°C has been introduced to ensure that the SLActive® surface achieves a fully mature surface when placed on the market.

The purpose of this post-market study is to re-confirm safety and performance of SLActive® implants produced under the optimized production process by monitoring crestal bone levels and adverse device effects and device deficiencies that could have led to a serious adverse device effect over time. As the highest incident of bone loss around implants is within the first 12 months according to literature (14), a follow-up of 12 months was chosen. SLA® (w/o ultrafine structure) will be used as a control device in this study. It was launched in 1994 and is considered to be one of the best-documented rough surfaces in implantology (15) (16). As mentioned earlier, SLActive® was associated with accelerated osseointegration properties (3) (4) (5) (6) (7) (8) (9) (10) (11). The osseointegration potential of SLActive® will be confirmed using a common method to assess osseointegration, resonance frequency analysis (RFA) (17) (with Osstell ISQ scale), and further investigated with regards to the underlying mechanisms by testing different osseointegration markers. In addition, the inflammatory and anti-inflammatory potential of the two surfaces will be assessed as inflammation plays an important role in osseointegration, particularly during the acute inflammatory response triggered in the early periods after surgery (18) (19) (20) (21).

Besides in-vitro studies (22) (23) (24), there were a few clinical studies performed looking at the expression of osseointegration markers on the SLActive® and SLA® surface (25) (26). Whereas Donos et al, observed an up-regulation of osteogenesis- and angiogenesis-associated gene expression on the SLActive® surface by day 7, Dolanmaz didn't find a difference between the two surfaces. Further clinical studies investigating osseointegration markers expression are

necessary to confirm the osseointegration potential of SLActive® shown in studies using RFA (11) (27) (28) analysis .

Inflammatory and anti-inflammatory markers are often assessed when comparing periodontitis patients with healthy patients (29) (30) (31). SLActive® has shown anti-inflammatory potential compared to the SLA® surface in in-vitro and pre-clinical studies (32) (22) (33) (34) but clinical data are still missing. Furthermore, no clinical studies investigating osseointegration markers and their correlation with inflammatory markers (cytokines) are known so far.

2 Objectives

2.1 Study Hypothesis

Based on previous obtained data the expectations are as follows:

Co-primary study hypotheses:

1) SLActive® implants are safe
2) 12 months after loading, the marginal bone loss around the SLActive® implants will not be appreciably greater than around the SLA® implants.

Secondary study hypotheses:

3) SLActive® implants show superior osseointegration compared to SLA® as tested by biomarker analysis
4) SLActive® implants show superior anti-inflammation compared to SLA® as tested by biomarker analysis

2.2 Primary Objective

The primary objective of this post-market study is to re-confirm safety and performance of SLActive® implants by means of bone level change 12 months after implant loading and monitoring of adverse device effects and device deficiencies that could have led to a serious adverse device effect.

2.3 Secondary Objectives

The secondary objectives of this study are to evaluate the osseointegration and anti-inflammatory potential of SLActive® implants compared to the SLA® surface. Implant stability (with ISQ) and osseointegration, inflammatory- and anti-inflammatory biomarker expression will be assessed during the early healing phase.

3 Study Design

3.1 Type and Design of the Study

This is a prospective single-blinded, randomized, paired sample, multi-center clinical study.

3.2 Indications and Contra-Indications

Straumann® Bone Level Tapered (BLT), Roxolid® SLActive® and SLA® 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.

Placing small-diameter implants (diameter 3.3 mm) in the molar region is not recommended.

Contra-Indications are:

- Non-completed jawbone growth, drug or alcohol abuse, allergies or hypersensitivity to chemical ingredients of materials used: titanium-zirconium alloy, all conditions which would be normally contraindicated for oral surgery.
- 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.

The complete details of the Instructions for Use (IfU) for the Straumann® Bone Level Tapered Roxolid® SLActive® and SLA® implants can be found in the Annex 1 and Annex 2.

3.3 Study Treatment

Patients will receive Straumann® Bone Level Tapered (BLT), Roxolid® implants with a SLActive® surface (test device) and a SLA® surface (control device) within the intended use (see IfU in Annex 1, Annex 2). Based on randomization (0), two different quadrants will be assigned for either control or test implant placement (study test and study control quadrant). Indications sites are premolars, molars and canines in mandible and maxilla and extraction need to have been performed more than 3 months ago (healed extraction sites). Implants will be 8, 10, 12 or 14 mm of length and with a diameter of 3.3 or 4.1 mm. Particular care should be used when placing small-diameter implants (diameter 3.3 mm) in the molar region.

Per patient, one control and one test implant will be appointed as study control and study test implant (“study implants”). An implant (test or control device) qualifies as study implant if the implant is assessed as primary stable (as defined in Section 7.2.3), the abutment torque is at least 15 Ncm at surgery and the implant site fulfills the eligibility criteria (canine to molar, extraction/ tooth loss more than 3 months ago, soft tissue grafting procedures more than 3 months and bone grafting procedures more than 6 months ago). If there are several control or test implants placed in a study quadrant which qualify as study implant, the most mesial implant satisfying all the criteria, will be appointed as study implant.

Screw retained abutments (SRA) of 2.5mm height will be placed at the same time as the implants and covered with a healing/ protective cap. The implants will be restored with a single crown or splinted restorations 10 weeks after implant placement (implant loading).

Further details can be found under 7.2 (treatment procedures)

3.4 Endpoints

3.4.1 Primary Endpoint

The following parameter will be measured as primary endpoint:

- Bone level change 12 months after implant loading.
- Occurrence of adverse device effects and device deficiencies that could have led to a serious adverse device effect

3.4.2 Secondary Endpoints

The secondary objectives assessed are:

- Bone level change (between implant placement and loading and between loading and 12 months after implant loading)
- Changes of biomarkers in GCF in regards to:
    - Inflammation (between implant placement and 30 days):

      Anti-inflammatory biomarkers analysis (concentrations of IL-10 and IL-4)

      Inflammatory biomarkers (concentrations of IL-6, IL-1β, TNF-α, IL-2)
    - Osseointegration (between day 7 and 8 weeks):

      Concentrations of VEGF, Osteocalcin (OCN), Osteopontin (OPN)
- Bacterial load analysis (between implant placement and 30 days)
- Implant stability (with ISQ) (between implant placement and 8 weeks)
- Soft tissue/ wound healing (Landry index) (between suture removal and 14 days)
- Clinical measurements
    - Keratinized tissue height at implant placement and after 12 months
    - Probing pocket depths (PPD) and Bleeding on Probing (BoP) after 12 months. It is not the idea to evaluate a change but rather the occurrence after 12 month and possible differences between groups as these parameters are an indicator to determine the incidence of peri-implant diseases.
    - FMPS (at screening and after 12 months)
- Implant survival
- Prosthetic success (prosthetic survival and mechanical complications acc. to ITI Treatment Guide Volume 8 (37))

- Patient satisfaction (OHRQoL, OHIP-14 questionnaire) (at screening, loading and after 12 months)

3.4.3 Safety

Safety will be assessed as described in Section 8

3.5 Study Sample Size

It is planned to enroll 60 patients into the study at 2 study centers. It is expected that both centers enroll approximately 30 patients (20 subjects at a minimum and 40 at a maximum). Details of sample size calculation are given in section 9.4.

3.6 Study Duration

The first patient was enrolled in the study in October 2019 and it is expected that recruitment will be completed after 12 months. Each patient will be followed for 12 months and implant loading and data will be collected during this time period. Hence, the end of the study is planned to be November 2021.

3.7 Study Population

The study population will consist of male or female patients, 18 years of age or older, who are in need of at least two dental implants (canine to molars, healed sites) placed in two different quadrants and meet all of the inclusion (Section 3.7.1) but none of the exclusion criteria (Section 3.7.2).

Patients must provide their written informed consent for study participation prior to any study related procedures (Section 7.1.1). Patients having signed the Informed Consent Form need to be entered in the Screening and Enrollment Log and are considered “enrolled” in the study. Patients who do not meet eligible criteria are considered “screening failures” (Section 11.3.6). Patients will be withdrawn from the study for the cases defined under 3.7.3.

3.7.1 Inclusion Criteria

The following criteria must be met for inclusion in the study:

- Males and females, at least 18 years old
- Partially edentulous patients in need of at least two dental implants (canine to molars) placed in two different quadrants in healed sites (3 months post extraction)
- Subject must have voluntarily signed the informed consent, are willing and able to attend scheduled follow-up visits, and agree that the encoded data will be collected and analyzed

3.7.2 Exclusion Criteria

The following exclusion criteria will lead to exclusion from the study:

- Any contraindications for oral surgical procedures
- Dental implant placement contraindicated according to Instructions for Use (IFU)
- Subjects with inadequate oral hygiene (FMPS ≥ 20%)
- Subjects who are currently heavy smokers (defined >10 cigarettes per day or >1 cigar per day) or who use chewing tobacco
- Subjects with drug or alcohol abuse
- Patients requiring soft tissue and bone grafting procedures
- Patients having had soft tissue grafting procedures within the last 3 months and bone grafting procedures within the last 6 months in the region where a study implant is planned
- Keratinized soft tissue height of less than 2 mm where a study implant is planned
- Inadequate bone volume
- Severe bruxism or clenching habits
- Woman who are pregnant or planning to become pregnant at any point during the study duration.
- patients who have systemic factors that could interfere with the healing process of either bone or soft tissue or the osseointegration process (e.g. bone metabolism disturbances, uncontrolled diabetes mellitus, anticoagulation drugs/ hemorrhagic diatheses)
- patients with local factors that could interfere with the healing process, such as untreated periodontal diseases, acute infection of implant site, temporomandibular joint disorders, treatable pathologic diseases of the jaw and changes in the oral mucosa)
- 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.

3.7.3 Withdrawal criteria

The Investigator must withdraw any patient from the study in the case of:

- No control and test implants received/ placed at visit 2
- No control and test implant (one of each) available that qualify as study implants (implant is assessed as primary stable (as defined in Section 7.2.3) at surgery, the abutment torque is at least 15 Ncm at surgery and the implant site fulfills the eligibility criteria, see Section 3.3 for further details), in 2 different quadrants.

The Investigator may withdraw any patient from the study in the case of:

- Non-compliance with the protocol
- Failure to attend the follow-up visits
- SAE or AE, which in the opinion of the Investigator prevents the patient's further participation in the study.
- Subject requires surgical treatment during the course of the study in the region of the mouth being evaluated in the study

Any patient may withdraw from the study any time without prejudice and will be offered an alternative treatment related to their dental condition. Patients 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 patient withdrawal will be documented on a Study Termination eCRF page and must include the reason for the patient withdrawal. Withdrawn patients will be replaced in case the recruitment is still ongoing. As soon as recruitment is completed withdrawn patients will not be replaced.

4 Device Description

4.1 Straumann Bone Level Tapered (BLT), Roxolid® implants

Straumann® BLT, Roxolid® implants are made of a titanium-zirconium alloy (commercial name Roxolid®) and are available with the SLActive® or SLA® surface. SLA® is a sandblasted, large-grit and acid-etched surface and SLActive® a hydrophilic and chemically active large grit sand blasted and acid etched surface (chemically modified SLA®). The chemically activated state is preserved by storage in a physiological sodium chloride solution. SLA® and SLActive® implants have the same macro and micro structure. However, there is a distinct difference in the nanometer scale between the surfaces. With the introduced postproduction-holding step all SLActive® implants show fully mature ultra-fine structures (UFS) when placed on the market.

The Straumann® BLT, Roxolid® implants considered for this study have the following dimensions: diameter (3.3, 4.1) and lengths (8, 10, 12, 14) as listed in Table 1.

The complete details of the product description and instructions for the Straumann® BLT, Roxolid® implants can be found in the "Basic information on the surgical procedures for the Straumann® Bone Level Tapered implant" (Annex 3) and in the respective IfU's (Annex 1, Annex 2).

Table 1: Description of the Implants

Material (core)*	Roxolid® (titanium-zirconium alloy)	
Surface*	SLActive®	SLA®
Device model image		
Implant Type	Bone Level Tapered (BLT)	
Implant diameter	3.3, 4.1 mm	
Implant lengths	8, 10, 12, 14 mm	
Packaging	in 0,9% NaCl solution	without solution

* In contact with human tissues / body fluids

The legal manufacturer of the device(s) is Institut Straumann AG, 4002 Basel, Switzerland.

4.2 Restorative Components

The clinician will select the appropriate restorative components and place the screw-retained abutment and healing cap as defined under study treatment (3.3) and prosthetic restoration (7.2.4).

- IfU of the screw-retained abutments (Annex 4): IfU Number 150.923: Straumann® Titanium Abutments and Temporary Abutments/Copings (Version J09 09/18)

4.3 Instruments

The surgical procedures are performed with the instruments listed in the brochure “Basic information on the surgical procedures for the Straumann® Bone Level Tapered implant”, Version en/E/00 02/17 (Annex 3).

4.4 Product Registration Status

The study devices, as well as the associated prosthetic components are CE marked. The products must be used within their intended purpose according to the respective IfU’s.

4.5 Instructions for Use, Handling and Labeling

Straumann® will provide the study centers with the necessary number of study devices for the study. The products delivered for the study are to be used only for the patients enrolled in the study and according to the protocol.

Device Deficiencies (DDs) shall be reported as described in Section 8.3.2

4.5.1 Instructions for Use (IfU)

The study devices must be used as described in the IfUs (Annex 1, Annex 2) and in the Brochures describing the surgical procedures (Annex 3).

- IfU Number 702049: Straumann® Dental Implants: Roxolid® SLActive® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level and Bone Level Tapered (Version D03 09/18)
- IfU Number 702107: Straumann® Dental Implants: Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level and Bone Level Tapered (Version B01 10/10)
- Basic information on the surgical procedures for the Straumann® Bone Level Tapered implant (490.038, Version en/E/00 02/17)

4.5.2 Handling

The study product should be stored in its original container until used and its access shall be controlled. The product will not be used if the sterile package is opened or damaged prior to use. The package will be discarded or returned to manufacturer with the enclosed implant if this is the case. Each implant is intended for use in one subject only and shall not be re-sterilized or reused. Reuse of single-use devices creates a potential risk of patient or user infection.

4.5.3 Labeling

The test device (SLActive®) will be relabeled specifically for use in this clinical study as an additional measure to ensure usage of SLActive® implants produced with the newly introduced production process.

4.6 Storage

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

4.7 Device Accountability

The Investigator must maintain an accurate and up-to-date accountability record of all study devices (BLT, Roxolid® implants) received, used for the study patients (not only the study control and study test implant), discarded (opened, but non-used) and returned during the course of the study. This information shall be recorded in the Device Accountability Record Log. Upon study devices receipt, the shipment records shall be signed by the site personnel.

The monitor will check the study device accountability for accuracy and completeness during the monitoring visits

At the end of the study, the monitor or Straumann's delegate conducting the closeout visit will guarantee the complete reconciliation of the device accountability.

4.8 Return of Study Device

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

5 Risk Evaluation

The current risk management report on implants (35) states a positive risk-benefit ratio for treatment of patients with the BLT Roxolid® implant system. Risk mitigation is performed as described in this report. Each of the risks assessed has been reduced as far as possible and is considered acceptable according to the defined acceptance criteria when weighed against the benefit level provided by the device, as described in the clinical evaluation report for BLT implants (36), according to its intended use, e.g. good performance and safety with respect to the restoration of function and esthetic oral rehabilitation for patients with missing teeth. Risks assessed specifically for the use of the BLT Roxolid® SLActive® and SLA® implants as detailed in the Risk Management Report (35) as well as in the respective instructions for use (Annex 1, Annex 2) are listed in the following and must be particularly taken care of during handling:

- Product can contains high number of UFS and this can lead to a toxicity reaction even though the likelihood is improbable
- Marking of position (inner configuration) on transfer piece might be rotationally incorrect (e.g. 45°) for bone level type implants and thus incompatible with the product

The optimization of the production process and the presence of UFS for SLActive® is not linked to any clinical performance or safety issue as concluded in the Rationale – Roxolid® UFS (37).

Overall, it can be concluded that the patients treated within this study are not exposed to risks other than the ones associated to oral implant surgery in general.

Refer to Table 5 for a list of potential expected Adverse Events and Adverse Device Effects following dental implant treatment.

6 Schedule of Assessments

An overview of the study procedures and evaluations is provided in Table 2. The evaluations are described in details in Section 7.

Table 2: Schedule of Assessments

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9
	Screening	**Implant Placement, sampling(baseline)**	**Sampling, suture removal**	**Sampling**	**Sampling,**	**Sampling, final impression**	**Loading**	**6-month follow-up**	**12-month follow-up**
	Up to 10 w before Implant Placement	**0**	**1 weeks (± 1 days)**	**2 weeks (± 2 days)**	**4 weeks (± 3 days)**	**8 weeks (± 5 days)**	**10 weeks (± 10 days)**	**6 months (±2 weeks) after loading**	**12 months (±3 weeks) after loading**
Informed consent	x								
If female, pregnancy test/disclaimer	x								
Patient eligibility	x	x (re-evaluation)							
Demographics	x								
Medical and dental history	x								
Concomitant medication and procedures	x								
Randomization[3]		x							
Documentation of surgery		x							
Oral hygiene (by FMPS)	x								x
KM (buccal)		x							x
PPD, BoP									x
X-ray (peri-apical)	x[1]	x					x		x
Patient satisfaction (OHIP-14)	x						x		x
Photograph of the implant site	x	x	x	x	x	x	x	x	x
Soft tissue (Landry index, buccal side)			x	x					
ISQ		x				x			
GCF fluid for Osseointegration (mesial side)			x	x	x	x			
GCF fluid for Inflammation (mesial side)		x[2]	x	x	x				
Samples for Bacterial load (one mesial, one distal)		x[2]	X	X	x				

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9
	Screening	**Implant Placement, sampling(baseline)**	**Sampling, suture removal**	**Sampling**	**Sampling,**	**Sampling, final impression**	**Loading**	**6-month follow-up**	**12-month follow-up**
	Up to 10 w before Implant Placement	**0**	**1 weeks (± 1 days)**	**2 weeks (± 2 days)**	**4 weeks (± 3 days)**	**8 weeks (± 5 days)**	**10 weeks (± 10 days)**	**6 months (±2 weeks) after loading**	**12 months (±3 weeks) after loading**
Implant survival			x	x	x	x	x	x	x
Documentation of final restoration							x		
Prosthetic success and survival								x	x
Pain relief (dose of Paracetamol)			x						
Final abutment torque						x			
Adverse events	x	x	x	x	x	x	x	x	x
Device Deficiencies		x	x	x	x	x	x	x	x
Changes in concomitant medication and procedures		x	x	x	x	x	x	x	x

[1] For screening a panoramic radiograph not older than 6 months should be available or one should be taken
[2] Sample to be taken 1 hour after surgery
[3] before implant placement but after the preparation of the bed where the first implant will be placed

6.1 Visit Windows

Patients need to be seen within the visit windows as stated in Table 3.

Table 3: Visit Days and Windows

Visit #	Visit Name	Visit Day and Window
Visit 1	Screening	Up to 10 weeks before implant placement
Visit 2	Implant placement, sampling (baseline)	Day 0
Visit 3	Sampling, suture removal	1 week (+/-1 days)
Visit 4	Sampling	2 weeks (+/-2 days)
Visit 5	Sampling	4 weeks (+/-3 days)
Visit 6	Sampling, final impression	8 weeks (+/-5 days)
Visit 7	Loading	10 weeks (+/- 10 days)
Visit 8	6-month FU	6 months (+/-2 week) after loading
Visit 9	12-month FU	12 months (+/-3 weeks) after loading

6.2 **Screening Visit** (Visit 1, up to 10 weeks before implant surgery)

Latest 1 day before the Screening Visit the Investigator (or designee) will review the study with the patient and invite him/her to participate (as described in Section 7.1.1). After written informed consent has been obtained, an evaluation will be conducted to determine whether the patient meets the study inclusion criteria and not any of the exclusion criteria and study specific information will be collected.

The following evaluations will be performed and documented at the Screening Visit, which are described in detail in **Section 7**.

- Before any study procedure starts, written informed consent from each patient has to be obtained according to the procedure described in Section 7.1.1
- If female, pregnancy disclaimer or test (see section 7.1.2 for further details)
- Patient eligibility (inclusion and exclusion criteria)
- Demographics
- Medical and dental history
- Concomitant medication and procedures
- Oral hygiene assessment (by FMPS)
- Panoramic radiograph except if one is available not older than 6 months
- Patient satisfaction (OHIP-14 questionnaire)
- AEs
- Photograph of the implant site

6.3 Implant placement, sampling (baseline) (Visit 2, day 0)

The eligibility criteria need to be re-evaluated prior to implant placement to confirm eligibility. Straumann® BLT, Roxolid®, SLActive® and SLA® implants need to be placed in the assigned study quadrants as described in Section 3.3 (study treatment) and Section 0 (randomization) and recommendations given by the manufacturer. Blinding is applicable as described in section 0. **Note**: if there is no control and test implant available (one of each) that qualify as study implants (implant is assessed as primary stable (as defined in Section 7.2.3) at surgery, the abutment torque is at least 15 Ncm at surgery and the implant site fulfills the eligibility criteria, see Section 3.3 for further details), in 2 different quadrants, the patient needs to be **withdrawn** (see section 3.7.3).

Surgical procedure, implant placement, final abutment insertion and postoperative patient instructions are performed and documented as described in section 7.2.3.

The following evaluations will be performed and documented at this Visit, which are described in detail in **Section 7**

- Review of the patient eligibility (inclusion and exclusion criteria)
- Randomization (before implant placement but after the preparation of the bed where the first implant will be placed, see Section 0 for further details)
- Documentation of surgical procedure and implant placement (see Section 7.2.3.)
- Periapical X-ray
- ISQ
- KM (buccal)
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site

1 hour after surgery:

- GCF fluid collection (mesial side) for inflammatory and anti-inflammatory biomarker analysis (7.3.2)
- Sample collection for bacterial load analysis

6.4 Suture removal and sampling (Visit 3, 1 week after implant placement)

Sutures will be removed, and the following evaluations will be performed and documented at this visit, which are described in detail in **Section 7.**

- Soft tissue / wound healing (by Landry index, buccal side)
- GCF fluid collection for inflammatory and anti-inflammatory biomarker analysis (mesial side)
- GCF fluid collection for osseointegration biomarker analysis (mesial side)
- Sample for bacterial load analysis (one sample mesial, one distal)
- Implant survival
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site
- Consumed dose of Paracetamol since surgery (for further details see 7.2.3)

6.5 **Sampling** (Visit 4, 2 weeks after implant placement)

The following evaluations will be performed and documented at this Visit, which are described in detail in Section 7.

- Soft tissue / wound healing (by Landry index, buccal side)
- GCF fluid collection for inflammatory and anti-inflammatory biomarker analysis (mesial side)
- GCF fluid collection for osseointegration biomarker analysis (mesial side)
- Sample for bacterial load analysis (one sample mesial, one distal)
- Implant survival
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site

6.6 **Sampling** (Visit 5, 4 weeks after implant placement)

The following evaluations will be performed and documented at this visit, which are described in detail in Section 7.

- GCF fluid collection for inflammatory and anti-inflammatory biomarker analysis (mesial side)
- GCF fluid collection for osseointegration biomarker analysis (mesial side)
- Sample for bacterial load analysis (one sample mesial, one distal)

- Implant survival
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site

6.7 Sampling, final impression (Visit 6, 8 weeks after implant placement)

The following evaluations will be performed and documented at this visit, which are described in detail in Section 7. **Before doing the final impression** (as described in section 7.2.4) the final abutment torque needs to be checked.

- ISQ
- GCF fluid collection for osseointegration biomarker analysis (mesial side)
- Implant survival
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site
- Final abutment torque (above or below 35 Ncm) of at least the study control and study test implant and implants involved in a splint with a study implant. **Note**: if the abutment torque of the study control or study test implant is below 35 Ncm it needs to be recorded as protocol deviation (see Section 11.4) as it will not be possible to load the implant after 10 weeks as defined (7.2.4)

6.8 Final Prosthesis / Implant loading (Visit 7, 10 weeks after implant placement)

Implants will be restored with single crowns or a splinted restoration in accordance to the defined study treatment (see Section 3.3) and recommendations given by the manufacturer. Prosthetic restoration is performed and documented as described in section 7.2.4. **Note**: if the final abutment torque was below 35 Ncm at the final impression visit (Visit 6) the implant should not be loaded.

The following evaluations will be performed and documented at this Visit, which are described in detail in Section 7

- Periapical X-ray
- Patient satisfaction (OHIP-14 questionnaire)
- Documentation of prosthetic restoration (see Section 7.2.4.)

- Implant survival
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site

6.9 6-month Follow-Up (Visit 8, 6 months after loading)

The following evaluations will be performed and documented at this Visit, which are described in detail in Section 7

- Implant survival
- Prosthetic success and survival
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site
- If a study implant was loaded with a temporary crown at visit 6: was the restoration exchanged with the final restoration at this visit or in between? If yes, specify the date and indicate the number of units and the implant positions of the implants/ teeth involved in the splint.

6.10 12-month Follow-Up (Visit 9, 12 months after loading)

The following evaluations will be performed and documented at this Visit, which are described in detail in Section 7

- Clinical measurements and oral hygiene assessment (PPD, KM (buccal), BoP, FMPS)
- Periapical X-ray
- Implant survival
- Prosthetic survival and prosthetic complications
- Patient satisfaction (OHIP-14 questionnaire)
- AEs and device deficiencies
- Changes in concomitant medications and procedures
- Photographs of the implant site
- If a study implant was loaded with a temporary crown at visit 7: was the restoration exchanged with the final restoration at this visit or in between? If yes, specify the date and

indicate the number of units and the implant positions of the implants/ teeth involved in the splint.

7 Study Procedures and Evaluations

7.1 Screening and Baseline Evaluation

7.1.1 Informed Consent

It is the responsibility of the Investigator, or an authorized person designated by the Investigator, to obtain informed consent (IC) from each patient participating in this study prior to any study related procedures. IC must be obtained before the evaluations of the screening visit (visit 1) start, as this is considered as first study specific procedure.

As part of the patient information, 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 and that data will be collected. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from the study at any time for any reason without prejudice. Ample time (at least 1 day before Visit 1) must be provided for the patient (e.g. document in the patient files the date when the patient is informed about the study) to read and understand the Informed Consent Form and to consider participation in the clinical investigation. Patients must read and understand the written patient information sheet.

The consent form must be personally signed and dated by the patient 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 patient. The electronic Case Report Form (eCRF) for this study contains a section for documenting informed consent, and this must be completed appropriately. The consent process must be documented in the patient file (source data). with the following data:

- Day the patient was informed of the study
- Day the patient was included in the study
- Date of screening visit
- ICF version that was signed
- Indicate that a copy of the ICF was given to the patient.

Patients having signed the Informed consent Form need to be entered in the Screening and Enrollment Log and receive a subject ID.

The informed consent must be approved by an Ethics Committee (EC) before consenting can begin. The Informed Consent Form must be available in the primary language of the patient. It is written in accordance with the "Declaration of Helsinki" (as adopted by the 18th World Medical Assembly, 1964, and as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), Edinburgh (2000), Seoul (2008), and Fortaleza (2013) (WMA General Assembly, 2013)), the regulation (EU) 2016/679 (General Data Protection Regulation) and applicable local regulations.

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 patients should be informed of the new information and be given a copy of the revised form. The patients must give their consent to continue the study, unless the patient was considered as a screening failure (see Section 11.3.6).

7.1.2 Pregnancy Test

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

If a woman becomes pregnant during the study, an AE form should be completed and the women should be followed as described in Section 8.5.

7.1.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be evaluated according to Sections 3.7.1 and 3.7.2 at screening and re-evaluated at implant surgery. Patients must fulfill all of the inclusion criteria and must not meet any of the exclusion criteria to be eligible for study participation. If this condition is not fulfilled the patient is considered a screening failure (11.3.6) and the Study Termination Form shall be completed.

7.1.4 Demographics

Subject demographics, including age, gender, and race/ethnicity, will be documented at the Screening Visit (Table 2). The ethnic origin will be recorded as Asian, European or Other.

For smoking status, subjects will be classified into

- never-smoker
- past smoker
    - 10 or more years since cessation

    - Less than 10 years since cessation
- current smoker
    - ten or less cigarettes per day
    - one cigar per day
    - more than ten cigarettes per day (note: exclusion criteria)
    - more than one cigar per day (note: exclusion criteria)
    - daily consumer of electronic cigarettes
    - non-daily consumer of electronic cigarettes

7.1.5 Medical and Dental History

Medical and dental history will be obtained at the Screening Visit (Table 2). Relevant medical history and current medical conditions will be evaluated by the Investigator based on the information available. The information may be obtained from the subject's general physician or from oral communication with the subject.

Medical History:

- history of radiotherapy
- history of periodontitis
- history of bisphosphonates usage
- If patient has been treated with systemic antibiotics, if "yes"; for how long
- history of a chronic infectious or inflammatory diseases
- history of controlled diabetes
- Other; specify

Dental History:

- Indicate in chart if tooth is missing or an implant already in place
- Indicate in chart where an implant is planned to be placed
- If tooth loss or extraction was > 3 month or <= 3 months ago for each planned implant site (**note**: tooth need to have been lost/ extracted more than 3 months ago in order that an implant site qualifies as possible study implant site)
- Reason(s) for tooth loss or extraction(s) for each planned implant site
- Other relevant dental history (e.g. performed bone augmentation procedures, prosthetic history)

7.1.6 Concomitant Medication and Procedures

Concomitant medication, procedures (non-study procedures), and supportive therapies will be recorded at the screening visit. Any changes in the concomitant medications, procedures, and supportive therapies must be documented on the respective page in the eCRF at each study visit until the end of the study.

7.1.7 Oral Hygiene

Adequate oral hygiene will be assessed prior to surgery using the Full Mouth Plaque Score (FMPS) according to O'Leary (for definition see 0). A FMPS of ≥ 20% will be defined as inadequate and leads to exclusion of the patient.

7.1.8 Panoramic radiograph

A panoramic radiograph must be available at the Screening Visit to assess the complete dentition and to use for surgical planning. The screening radiograph can be taken during the Screening Visit or be available from a previous date within 6 months.

7.2 Patient Treatment Procedures

7.2.1 Randomization

Assignment of one study test (placement of SLActive® implant(s)) and one study control quadrant(s) (placement of SLA® implant(s)) (=study quadrants) will be based on randomization at surgery visit, before implant placement but after the preparation of the bed where the first implant will be placed.

If there are two quadrants (suitable for study required implant placement) available in the same arch, those two quadrants will be selected for randomization. If this is applicable for the upper and lower arch the study site can select the arch for randomized. The randomization will be “left/ right” to assign test/control treatment).

If the two available quadrants (suitable for study required implant placement) are from different arches the randomization will be “upper/ lower” to assign test/control treatment.

Two quadrants available in the same arch: -> randomization left/ right

o	o
(o)	

o	o
	(o)

If:

o	o
o	o

-> The site selects the arch for randomization

The two available quadrants are from different arches: -> randomization upper/ lower

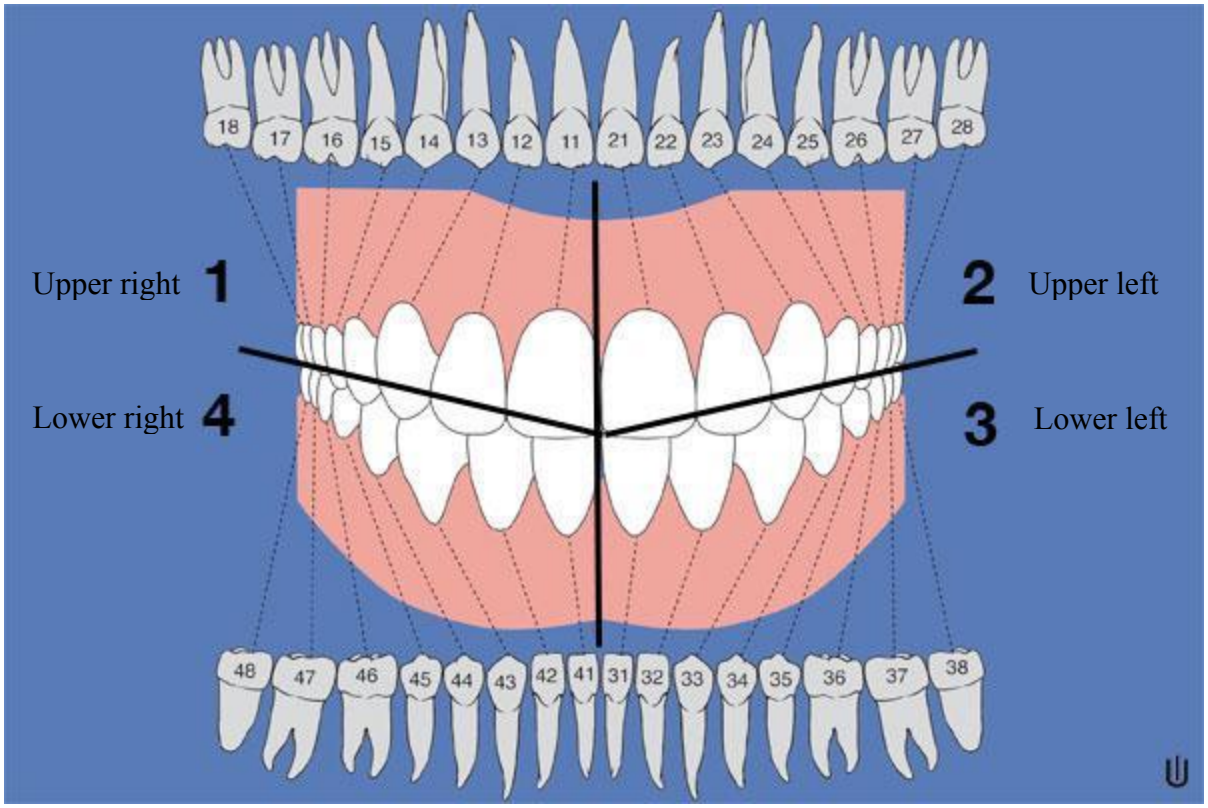
o	
	o

o	
o	

Randomization of eligible subjects will be performed using an Electronic Data Capturing (EDC) system. After log into the EDC system and entering the suitable quadrants for study required implant placement the system determines the treatment allocation. In case it’s not possible to access the EDC system at site the Contract Research Organization (Factory) can provide the randomization arm.

The randomization in the EDC is programmed by Data Management. A block randomization process will be applied to randomize each center separately. Additionally, the randomization will be stratified for randomization in the same arch or in different arches, therein 2 randomization lists will be produced.

Quadrant I-IV are defined as:



The randomization code is a five digit number, consisting of the center number (e.g. 1 or 2), the individual patient number (01, 02, 03,…) and the randomization list number (01, 02). No access to the master randomization list will be available to the study centers, the external Monitors, the subjects and the Straumann non-Clinical-Research project team.

The study control and study test implant will be defined as described in Section 3.3

7.2.2 Blinding

The assessment and the measurements will be performed by a separate person, not the operator. The patient will not know in which quadrant SLActive® or SLA® implants are placed.

7.2.3 Surgical procedure & documentation and postoperative instruction

Surgical procedure:

Preoperative systemic antibiotic (2 g Amoxicillin) prophylaxis will be provided 1 h prior to surgery if necessary. Mid-crestal incision and elevation of a minimal mucoperiosteal flap will be made. The incision will be further extended crestally or with releasing incisions where needed. The implant shoulder should be placed 1 mm subcrestal and the ridge flattened if reasonable. Healing will be transgingival. Implants, screw retained abutments and healing cap will be placed at surgery as defined under Study Treatment (section 3.3).

Surgical documentation:

At the surgery visit (Table 2), the following needs to be documented **for all BLT, Roxolid® implants placed** during the surgery visit:

- Bone quality according to the 4 different bone types described by Lekholm et al., 1985
- Details of the surgery (including site of implant placed (FDI position))
- Implant placed (article number and dimensions)
- Insertion torque measurements if applicable
- Stability of the implant after placement. The implant can be considered as primary stable or instable by the investigator (assessed by hand testing).
- Abutment torque
- Defined study control and study test implant. Note: As defined in Section 3.3, the most mesial implant (test or control device), which qualify as study implant (implant is assessed as primary stable, the abutment torque is at least 15 Ncm at surgery and the implant site fulfills the eligibility criteria (canine to molar, extraction/ tooth loss more than 3 months ago, soft tissue grafting procedures more than 3 months and bone grafting procedures more than 6 months ago)) will be appointed as study control and study test implant.
- Details (article number) of provided restorative components (screw retained abutment (SRA), healing caps etc.).
- Occurrence of complications related to the treatment (e.g. implant placement or prosthetic restoration). Report as AE/ADE

Note: if there is no control and test implant available (one of each) that qualify as study implants (implant is assessed as primary stable (as defined in Section 7.2.3) at surgery, the abutment torque is at least 15 Ncm at surgery and the implant site fulfills the eligibility criteria, see Section 3.3 for further details), in 2 different quadrants, the patient needs to be **withdrawn** (see section 3.7.3). If primary stability of any implant not given this needs to be reported as ADE.

Postoperative patient instruction:

Postoperative, patient will be provided with Paracetamol and instructed to take 1g every 8 hours if needed (for pain relief). Final dose will be recorded 7 days after surgery

7.2.4 Prosthetic restoration and Documentation

Description of prosthetic restoration:

The final prostheses (single crown or splinted, metal-ceramic) is done according to the usual procedure of the clinic. However, the prostheses will only be provided and loaded 10 weeks after surgery (Visit 7) if the abutment torque was above 35 Ncm before taking the final impression at visit 6. The implants can be loaded with a temporary crown in occlusion at the discretion of the investigator (for example if the study implant was planned to be part of a bridge and the non-study implant can't be loaded the study implant can be loaded with a temporary crown in occlusion).

Prosthetic Documentation:
Details of the final restoration need to be documented at Visit 7 (Table 2) for the study control and study test implant:

- Whether loading of the study control and study test implant is performed at visit 7. **Note**: if loading of the study control or test implant is not performed at this visit it needs to be recorded as protocol deviation 11.4.
- The type of restoration for the study control and study test implant: loading with the final prostheses (single crown / splinted, material: titanium / cobalt chrome) or loading with a temporary crown in occlusion (specify the material and the reason for loading with a temporary crown). If splinted, indicate the number of units and the implant positions of the implants/ teeth involved in the splint.
- Occurrence of complications related to the prosthetic restoration. Report as AE/ADE

7.3 Outcome Assessments

The time points for the assessments are listed in Table 2 (schedule of assessment) and are performed on the **study control and study test implant** if implant specific.

7.3.1 Peri-apical Radiographs and Bone Level Change

7.3.1.1 Peri-apical Radiographs

For bone level assessment standardized peri-apical radiographs are taken at the time points listed in Table 2 (schedule of assessment) .

7.3.1.2 Mean Implant Bone Level Changes

On the standardized peri-apical radiographs mesial and distal implant bone levels will be evaluated. The reference point for the bone level measurement is the implant shoulder. The bone level will be measured as the distance between the implant shoulder and the first visible bone contact on the implant. The bone level will be measured on the mesial and distal aspect of the 2 study implants. Mean bone level changes between two time-points will be computed by subtracting the average bone level from one visit with the other.

In this study, the time point and number of X-rays do not differ from the standard daily practice used for implant patients outside this study.

Original, full X-ray and photographs need to be saved in patients files.

A shared server has been made available to the study site for upload following pseudonymization. Files should be saved in their original resolution, ideally in .tiff format. The X-ray should include neighboring teeth and the entire implant length and include the following information:

- Study ID (CR 2017-05)
- Patient ID
- Visit #
- Date of visit
- Study implant location (FDI)

Any additional information present on the original X-ray needs to be removed before upload onto the shared server.

A blinded expert will perform the bone level measurements on the X-rays according to the X-ray evaluation protocol. Measurements will take into account distortion based on changes on the radiograph from the true dimension of the implant.

7.3.2 GCF collection and biomarker analysis

7.3.2.1 GCF collection and processing for biomarker analysis

GCF samples will be obtained using the filter paper technique. After removing the supra-gingival biofilm with sterile cotton rolls, the sampling place (mesial side of the study control and study test implant) will be isolated with cotton rolls and gently air-dried 1 minute before sampling in the aim to eliminate any potential contamination with saliva. A paper strip of standard length and height (Periopaper, Pro Flow, Amityville, NY, USA) will be inserted into the gingival/peri-implant sulcus/pocket until mild resistance was felt and left in place for 30 seconds.

Sampled fluid volume will be measured with a calibrated Periotron 8000 or 8010 (Interstate Drug Exchange, Amityville, NY, USA). Then the strips will be inserted in micro-centrifuge plastic tubes. The tubes will be placed on ice until all samples have been collected, after which the tubes will be stored at −80°C until biochemical analysis at Universidad Complutense. Samples collected at other study centers will be shipped to Universidad Complutense by a cold chain transport before analysis. The transportation will take place on the same day, the temperature during transportation will be -80°C, and the package will be equipped with a temperature tracking device for quality purposes.

Inflammatory, anti-inflammatory and osseointegration markers will be measured through appropriate human immunoassays using a calibrated luminometer. Results will be analyzed using clinical diagnostic software and will be expressed as picograms per milliliter.

7.3.2.2 Biomarker analysis

Interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α and IL-2 will be measured from the obtained GCF samples as markers of inflammation and IL10 and IL-4 as markers for anti-inflammation, VEGF, Osteocalcin and Osteopontin will be measured as markers of osseointegration. To prepare the samples, 200ul of a phosphate buffer solution will be added to each tube. The samples will be incubated during 30 minutes at room temperature and then will be centrifuged for 10 minutes at 10.000rpm. The concentration of the markers will be measured through high-sensitivity multiplex human immunoassays (HSTCMAG-28K, Merk for the inflammation / anti-inflammation, HBNMAG-51K for OPG and OCN and HAGP1MAG-12K for VEGF, Merk) at Universidad Complutense.

7.3.3 Bacterial sample collection and bacterial load analysis

Pooled subgingival samples will be obtained at the mesial and distal side of the study control and study test implant from each patient. Samples will be taken with two consecutive sterile

medium paper-points (#30, Maillefer, Ballaigues, Switzerland) that were kept in place for 10 s and then transferred into a screw-capped vial. The vials will be kept on ice until they will be transported to the microbiology laboratory within 2 h and stored in deep freezing (-20ºC).

Analysis of bacterial load will take place at Universitad Complutense.

Samples collected at other study centers will be shipped to Universidad Complutense by a cold chain transport before analysis. The transportation will take place on the same day, the temperature during transportation will be -20°C, and the package will be equipped with a temperature tracking device for quality purposes.

Samples will be processed for quantitative PCR for detection of total anaerobic counts and counts of selected periodontal pathogens (*A. actinomycetemcomitans*, *Tannerella forsythia*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*). Data will be expressed in colony-forming units (CFU) per mL of the original sample.

7.3.4 Implant Stability (with ISQ)

Implant stability will be assessed by ISQ (implant stability quotient) measurement with an Osstell device. ISQ is a resonance frequency analysis (RFA) method.

The ISQ scale correlates with micromotion, with the higher the ISQ value, the more stable the implant. The Osstell ISQ is an instrument that measures the resonance frequency of a SmartPeg when it is attached to an implant or to an abutment attached to an implant. The resonance frequency is calculated into an ISQ-number (Implant Stability Quotient), ranging from 0 to 100. The Osstell ISQ instrument vibrates the SmartPeg through magnetic pulses and measures the resonance frequency of it.

7.3.5 ISQ measurement

The Osstell device will be used according to the manufacturer’s instructions. In short, the SmartPeg will be attached to the final abutment. It needs to be ensured that the correct type of SmartPeg is used based on the abutment type. To function properly, the SmartPeg needs to be attached properly to the abutment; however no excessive forces should be used to screw it onto the abutment since this could damage the SmartPeg. The hand-held probe will be used to magnetically stimulate the SmartPeg. Two measurements will be taken; one with the probe held perpendicular to the jaw line, and the second with the probe in line with the jaw line.

To ensure that the measurements at the two time-points can be compared with each other, it is important that they are performed with the abutment screwed in at the same torque. Therefore, on the day of surgery, the abutment is placed at the torque between 15Ncm and 35Ncm and

ISQ measurement is performed. At 8 week after surgery, ISQ measurement is performed with the abutment at the same torque, after which the abutment is brought to its final torque.

7.3.6 Soft tissue/ wound healing assessment

Soft tissue healing will be assessed at the **buccal** side of the implant according to the Soft Tissue Healing Index by Landry (1988). The index is defined as follow:

Healing Index 1 - Very Poor (has 2 or more of the following):

(1) tissue color: >= 50% of gingiva red

(2) response to palpation: bleeding

(3) granulation tissue: present

(4) incision margin: not epithelialized, with loss of epithelium beyond incision margin

(5) suppuration present

Healing Index 2 – Poor:

(1) tissue color: >= 50% of gingiva red

(2) response to palpation: bleeding

(3) granulation tissue: present

(4) incision margin: not epithelialized, with connective tissue exposed

Healing Index 3 – Good:

(1) tissue color: >= 25% and < 50% of gingiva red

(2) response to palpation: no bleeding

(3) granulation tissue: none

(4) incision margin: no connective tissue exposed

Healing Index 4 - Very Good:

(1) tissue color: < 25% of gingiva red

(2) response to palpation: no bleeding

(3) granulation tissue: none

(4) incision margin: no connective tissue exposed

Healing Index 5 – Excellent:

(1) tissue color: all tissues pink

(2) response to palpation: no bleeding

(3) granulation tissue: none

(4) incision margin: no connective tissue exposed

7.3.7 Clinical measurements

7.3.7.1 Probing Pocket Depth (PPD)

The PPD will be measured around the implant by recording the distance in millimeters from the gingival margin to the bottom of the pocket at 4 locations (mesial, buccal, distal, and palatal).

7.3.7.2 Height of keratinized mucosa (KM)

The width of the keratinized tissue will be measured at the **buccal** side of the implant.and expressed in mm. At surgery the measurement will be performed for all implants placed at 12 months follow-up only for the study control and study test implant

7.3.7.3 Bleeding on Probing (BoP)

Bleeding on probing (BoP) will be recorded according to Lang et al. 1986. The presence or absence of bleeding on probing (BoP) will be documented as a “yes” or “no” on 4 sites (mesial, buccal, distal, and palatal) around the implant.

7.3.7.4 Full Mouth Plaque Score (FMPS)

The Full Mouth Plaque Score (FMPS) according to O’Leary et al (39) should be documented as an indicator for the oral hygiene on each single tooth of the mouth mesial, buccal, distal and palatal.i Disclosing agents should not be used to assess plaque.

The FMPS will be assessed with the following formula:

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

7.3.8 Implant Survival

Implant survival will be defined as follows:

A surviving implant is defined as an implant in place at the time of the follow-up. Any implant loss shall be assessed as an early loss (implant fails before being osseointegrated) or late loss (after being osseointegrated).
The basis for implant survival analysis are the study control and study test implants within the ITT population. Implant losses of the other implants will be recorded as AE’s.

7.3.9 Prosthetic Success and Survival

During the prosthodontic examination, the implant supported prostheses of the study control and study test implants will be examined for any complications and failures. Mechanical complications are defined in the ITI Treatment Guide Volume 8 (40).

Mechanical complications may be:

- Loss of retention
- Fracture and/or chipping
- Fracture of framework
- Loosening of occlusal screw
- Fracture of occlusal screw
- Loosening of abutment

A failure is defined as an event leading to: the loss of the reconstruction.

Complications and failure of prostheses from all implants placed at surgery will be recorded under the normal AE reporting (see also mechanical complications listed as potential expected Adverse Events and Adverse Device Effect in Table 5).

7.3.10 Patient satisfaction

Oral Health Related Quality of Life (OHRQoL) will be assessed using Oral Health Impact Profile (OHIP-14). In the present study, the Spanish translation, as applicable, of the short form OHIP-14 will be used. The OHIP-14 is derived from the original OHIP-49, which was introduced by Slade and Spencer in 1994. It is an instrument that was specifically designed to measure the impact of oral disorders on OHRQoL. It contains 49 items of seven domains (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap). The OHIP-14 contains 14 questions in these seven domains and proved to be sensitive to changes in prosthetic treatment and oral health. For each of the questions, subjects are asked how frequently they have experienced the event during the last month. Responses are given on a Lickert scale (0 – never, 1 – rarely, 2 – occasionally, 3 – frequently, 4 – very frequently, 5 – always). A high OHIP score indicates a low OHRQoL (41).

7.3.11 Photograph of the implant site

Digital photographs should be taken as follows if possible:

- Intraoral pictures (at least from the study control and study test implants/ implant position):
    - At each study visit V1-V9
    - At implant placement (V2):
        - After the preparation of bed of the first implant to be placed
        - After insertion of implants
    - At loading (V7):
        - After insertion of the final crown

- Extraoral pictures: maximum smile position, frontal and lateral view
    - Screening visit (V1)
    - 12-month follow-up (V9)
- The digital images should be labeled with subject's study ID and visit data, including concise explanatory text.

7.3.12 Adverse Events

Adverse Events (AE) collection for each patient will start at Screening Visit and ends after a patient withdraws from the study or completes the final study visit. At each visit, the Investigator should determine if any adverse events occurred since the last study visit by inquiring with the patient and reviewing any dental and medical records. These AEs, along with any AEs from the current study visit, should be documented on the appropriate eCRF form (specifying the region/ implant position(s) concerned or related to (for a procedure) and using the AE terms from Table 5 if applicable) and reported as described in Section 8 of the protocol. In addition the Investigator should evaluate the status of any ongoing AEs throughout the study as specified in Section 0.

7.3.13 Device Deficiencies

Device Deficiencies will be recorded for all Straumann products used for the treatment (including prosthetic components and instruments). Device Deficiency collection for each patient will start at Visit 2 (surgery visit) and ends after the last study required treatment.
If a DD leads to an AE (e.g., bleeding, pain, swelling, infection, peri-implantitis) or SAE (e.g., nerve encroachment, sinus perforation, etc.) the respective adverse event eCRF form should as well be completed and the process for adverse events followed (as described in Section 7.3.12 above).
DDs should be documented on the appropriate eCRF form (specifying the article number and Lot.nr of the device concerned and the implant position if applicable) and reported as described in Section 8 of the protocol.

8 Evaluation of Adverse Events and Device Deficiencies

8.1 Definition

A summary of the classification for AEs according to ISO 14155:2011 is provided in Table 4.

Table 4: 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 (42)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

8.1.1 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 patients, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device, or events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices. Disease signs and symptoms already existing prior to the use of the study devices are not considered as AE (but as medical history instead, as described in Section 7.1.5) unless they re-occur after the patient has recovered from the pre-existing condition, or represent an exacerbation in intensity or frequency.

AEs will be collected as described in Section 7.3.12.

8.1.2 Serious Adverse Event (SAE)

An AE should be classified as serious if it meets any of the following criteria:

- Led to a death;
- Led to a serious deterioration in the health of the patient, 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.

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 (SAE).

8.1.3 Device Deficiency (DD)

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

DDs that did not lead to an AE/SAE but could have led to an SAE if:

- suitable action had not been taken, or
- intervention had not been made, or
- circumstances had been less fortunate.

(DDs with SADE potential) are reported as specified for serious adverse events (SAEs/SADEs) in Section 8.3.1. Device Deficiencies will be classified into:

- DDs with Serious Adverse Device Effect (SADE) potential
- DDs without SADE potential

Device Deficiencies will be collected as described in Section 7.3.13. DDs that lead to an AE/SAE will be recorded on the adverse event form as well.

8.1.4 Adverse Device Effect (ADE)

An ADE is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instruction 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 AE which has even a possible relationship to the investigational device will be classified as an ADE.

8.1.5 Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (see Section 8.1.2).

8.1.6 Unanticipated Serious Adverse Device Effect (USADE)

An USADE is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the Risk Management Report (35), IfU (Annex 1, Annex 2) or Table 5 in the current protocol. The term “unexpected” is considered as equivalent to “unanticipated”.

8.1.7 Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is an SADE which by its nature, incidence, severity or outcome has been identified in the Risk Management Report (35) or IfU (Annex 1, Annex 2). The term “expected” is considered as equivalent to “anticipated”. For a compiled list of expected events see Table 5 “Listing of expected AE’s and ADE’s”.

8.2 Assessment of Adverse Events and Device Deficiencies

Each AE should be assessed by the Investigator or another suitably qualified clinician who is trained in recording and reporting AEs and has been delegated to this role (such delegation must be captured in the Site Signature and Delegation of Authority Log) for seriousness, relationship to the investigational device or the procedure and severity as described in this chapter. A rationale shall be provided (short narrative) for each assessment.

Sponsor will review the investigator's assessment of:

- all adverse events and determine and document in writing their seriousness and relationship to the investigational device and procedure
- all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect

In case of disagreement between the sponsor and the principal investigator(s), both opinions will be communicated to concerned parties. The sponsor will evaluate the AEs for expectedness as described in Section 8.2.7

8.2.1 Seriousness

An AE will be described as serious if it meets the definition in Section 8.1.2.

8.2.2 Relationship to the investigational device

The Investigator should assess the relationship of the AE to the investigational device. In this study only the study implants (study control and study test implant) need to fulfil the protocol requirements, thus the relationship will be assessed to the study implant (=investigational device). Consequently, **AE’s at implant positions of study implants** need to be assessed for relationship to the investigational device (study implant).

The relationship should be assessed using the following categories:

- Related – there is a reasonable causal and temporal relationship between the treatment with the investigational device and the AE.

- Possibly related or unknown – The relationship between the treatment with the investigational device and the adverse event is less likely; however, the determination that there is no relationship cannot be made or is unknown.
- Not related – no relationship between treatment with the investigational device and the AE is obvious.

8.2.3 Relationship to the Procedure

The Investigator should assess the relationship of the AE to the procedure (dental implant treatment, which involves implant placement and prosthetic restoration). In this study, this mean any procedure related to **dental study implant treatment**. The relationship should be assessed using the categories described in Section 8.2.2.

8.2.4 Severity

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

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

The term “severe” used to describe the intensity of an event should not be confused with the term “serious”, as defined in Section 8.1.2.

8.2.5 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 ADE, especially that of an SAE/SADE.

8.2.6 SADE potential

Each DD that did not lead to an AE/SAE should be assessed by the Investigator for its Serious Device Effect (SADE) potential as defined in Section 8.1.3.

DDs that lead to an AE/SAE will be recorded on the adverse event form as well.

8.2.7 Expectedness (Anticipation)

For each ADE and AE’s at or related to an implant position where a BLT Roxolid® implant was placed during surgery or there is a temporal relationship to a dental treatment procedure the sponsor (including at least one medical expert) will determine whether the event is anticipated (expected) or unanticipated (unexpected) based on knowledge of the reaction and any relevant product information as documented in the IfUs (Annex 1, Annex 2), the risk management report for implants (35) or in the list of potential expected AEs and ADEs in the current protocol (Table 5), without claim to completeness. The event will be classed as either:

- **Expected** – the reaction is consistent with the effects of the device listed in the Risk Management Report, IFU or the list of potential expected AEs and ADEs in the current protocol (**Table 5**).
- **Unexpected** – the reaction is not consistent with the effects listed in the Risk Management Report, IFU or the list of potential expected AEs and ADEs in the current protocol (**Table 5**).

An expected ADE can become an unexpected ADE, if there is a change in either the severity, outcome or occurrence of the ADE.

Table 5: List of Potential Expected Adverse Events and Adverse Device Effects following dental implant treatment

Dental implant treatments involves implant placement and prosthetic restoration. The table includes AEs and ADEs expected for implant treatment in general and specifically for procedures related to the implant or abutment, without claim to completeness.

Biological complications	**Implant**	**abutment**
General		
• Bruising	x	
• local inflammation	x	x
• Local irritation	x	x
• Swelling	x	
• Infection at implant site without suppuration (local)	x	x
• Infection at implant site with suppuration (=peri-implant abscess, local)	x	x
• Gingival enlargement (=gingival hyperplasia, gingival hypertrophy, gum overgrowth, hypertrophic gingivitis)	x	
• Gingival recession (=dehiscence of the gingiva, receding gums)	x	
• Exfoliation (in connection with the dental implant)	x	
• Pain	x	
Hard tissue related		
• Low primary stability (at surgery)	x	
• Implant mobility (tactile horizontal or vertical)	x	
• Early loss/failure of implant (i.e. before osseointegration)	x	x
• Late loss/failure of implant (i.e. after osseointegration)	x	x
• Radiolucency	x	
• Bone necrosis	x	
• Bone damage/ fracture	x	x
• Delayed healing/osseointegration	x	
• Excessive bone resorption/bone loss*	x	
Systemic complications		
• Asphyxiation	x	x
• Anaphylaxis	x	x
• Slowed recovery after treatment	x	
• Implant obstructs patient airway	x	
• Allergic reaction/ hypersensitivity to implant material	x	
• Allergic reaction/ hypersensitivity to abutment material		x
• Toxicity reaction	x	x
• Systemic infection	x	x
Other		
• Foreign body sensation	x	
• Oro-sinus or oro-nasal intrusion/fistula	x	
• Permanent paresthesia, dysesthesia	x	
• Chronic pain	x	
• Nerve damage in the jaw	x	
Mechanical complications	**Implant**	**abutment**
• Implant cannot be placed	x	
• Loosening of abutment	x	x

• Loosening of occlusional screw	x	x
• Loss/ failure of prosthesis/ reconstruction		x
• Loss/failure of an healing cap		x
• Fracture/ breakage of abutment		x
• Fracture of occlusional screw		x
• Fracture of implant	x	
• Fracture/ chipping of prosthesis / framework	x	x
• Implant connection is damaged and non-restorable	x	
• Abutment cannot be fixed properly on the implant	x	x
• Jamming of abutment		x
• Screw does not fit properly	x	x
• Stuck screw	x	x
• Bridge does not fit	x	x
• The Crown does not fit		x
• Coping or protective cap does not fit		x
• Corrosion of the abutment		x
• Irreversible damage to adjacent/opposing teeth or unfavorably affected adjacent teeth	x	
• Loss of cement retention (of prosthesis)		x
Other complications	**Implant**	**abutment**
• Esthetic problem/poor aesthetic outcome	x	x
• Jaw fracture	x	
• Phonetic difficulties	x	x
• Aspiration of implant	x	
• Swallowing of implant	x	
• Aspiration of abutment		x
• Swallowing of abutment		x
• Aspiration of component other than implant and abutment. Specify component		
• Swallowing of component other than implant and abutment. Specify component		
• Implant burned to mucous membrane (through MRI energy)	x	
• Abutment burned to mucous membrane (through MRI energy)		x

* Based on the 1st European Workshop on Periodontology an average marginal bone loss (MBL) of less than 1.5 mm within the 1st year after the insertion of the prosthesis was specified as criteria for measuring success (43). Based on this information the central radiologist will flag any bone level changes greater than 1.5 mm between implant loading and the 12-months follow-up visit. 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.

8.3 Procedure for Reporting Adverse Events and Device Deficiencies

The procedure for the reporting of adverse event and device deficiency reporting is detailed in flowchart 1.

8.3.1 Adverse Event Reporting

In case of an occurrence of an AE assessed as non serious, the Investigator will complete the appropriate eCRF form within 30 days of awareness of the event-

In case of an occurrence of an AE assesses as serious (SAE), the Investigator shall inform the sponsor **within 24 hours of awareness of the event** by completing the SAE form in the eCRF and / or by writing an email to clinicalresearch@straumann.com.

The Sponsor will report any SAE to the EC within 7 days of awareness of the event by email to the following address: ceic.hcsc@salud.madrid.org.

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 any SAE as soon as he/she has knowledge of the event within the above timeframe irrespective of when the actual event occurred.

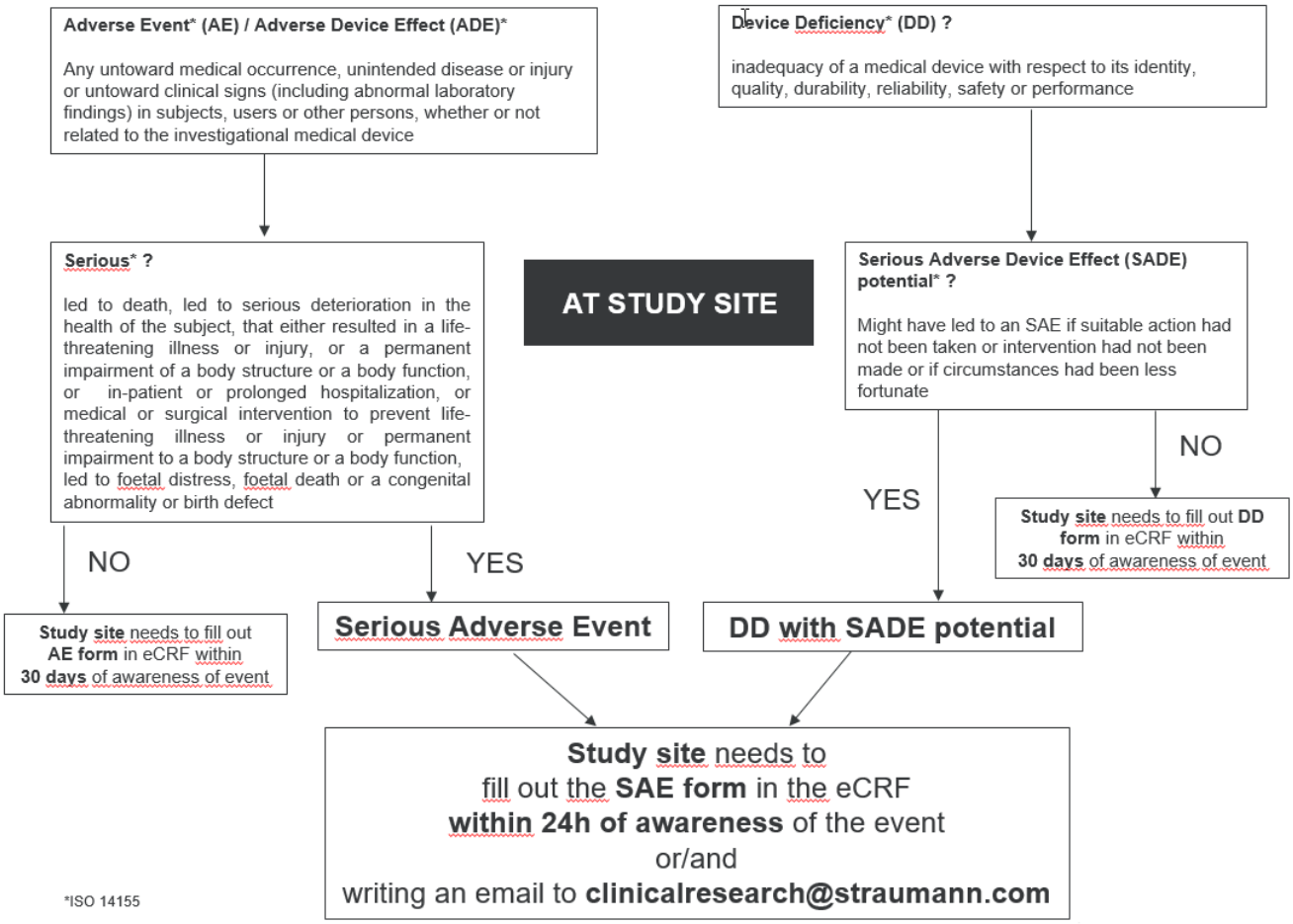
If an SAE constitutes a serious incident or a serious public health threat, the additional steps detailed in flowchart 1 will be followed.

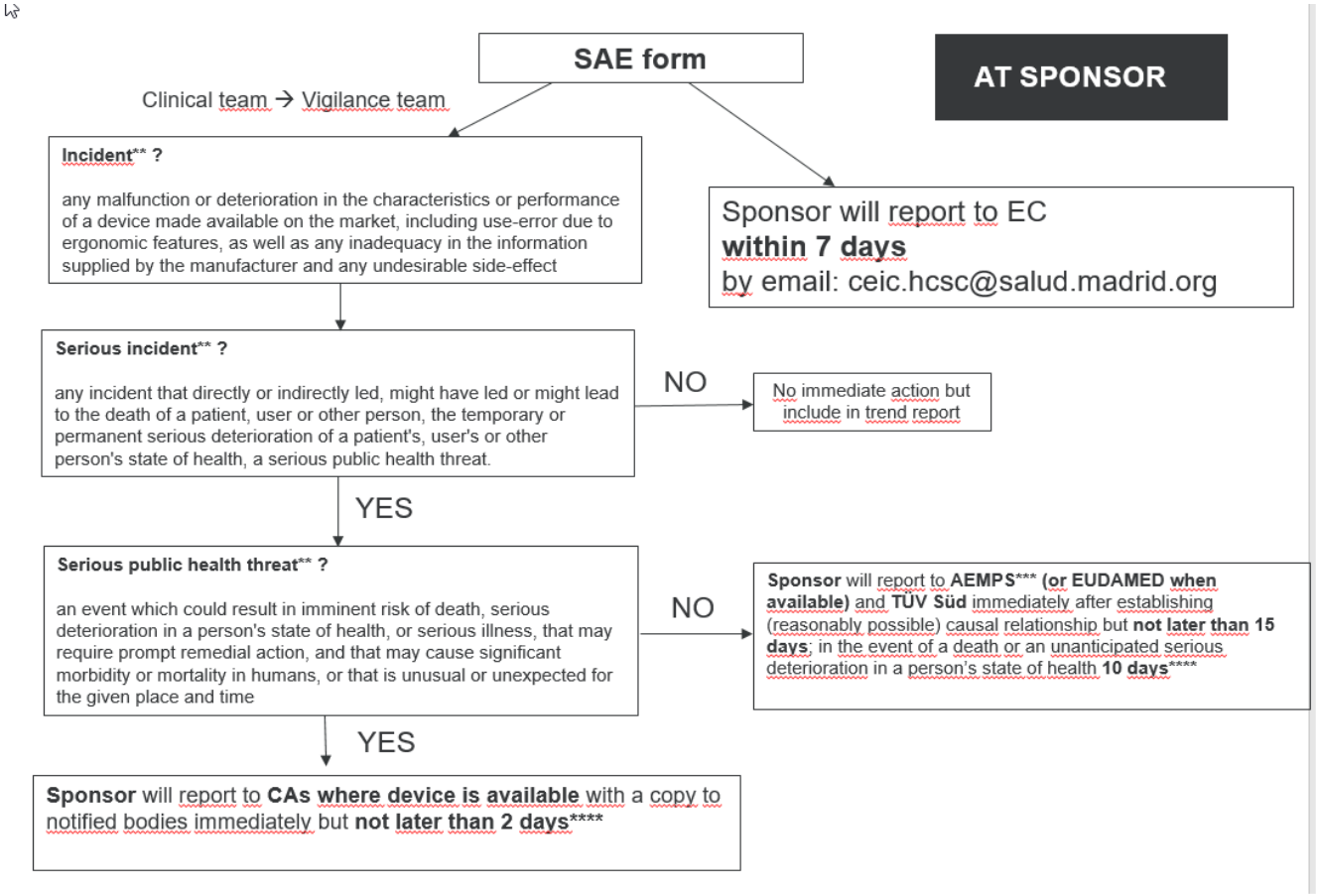
8.3.2 Device Deficiency Reporting

DDs without SADE potential should be reported by the investigator to the sponsor within 30 days of awareness of the event using the Device Deficiency Form.

DDs with SADE potential shall be reported the same way as SAEs (see previous paragraph).

Flowchart 1: Adverse event and device deficiency reporting





**MDR; ***Agencia Española de Medicamentos y Productos Sanitarios; ****Straumann procedure QMS-CORP-000297, in line with MDR

8.4 Monitoring of Patients 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 devices.

The outcome of an event will be pursued until resolution or until the last data queries are issued following the patient's last study visit. For screening failures, ongoing AEs, ADEs and DDs must be followed and updated until the date the patient is deemed a screening failure. For patients 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.

8.5 Pregnancy

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

9 Statistical Considerations

An independent qualified statistician will perform all statistical analyses.

The primary analysis will be conducted after all patients completed the 12-month follow-up visit. Optional interim analysis will be performed, as described in the SAP, after completion of the 8 weeks follow-up visit.

9.1 Statistical analysis

Descriptive summary statistics will be computed for all parameters documented in the case report forms (eCRF). Quantitative parameters will be described by seven-point scales with mean, standard deviation, median, quartiles, minimum and maximum. For qualitative variables absolute and relative frequencies will be given. All descriptions will be done separately for treatment groups and visits. Subjects who terminate the study prematurely will be included in the ITT population. Missing values of the primary and secondary outcomes will not be imputed. Detection of outliers should occur during the blind data review and it should be decided there on how to handle them.

The frequency and percentage of subjects in each population, study withdrawals, subgroups and major protocol deviations will be presented.

The assessment of protocol deviations will be made during a data review meeting. Major protocol deviations will lead to an exclusion from the Per-Protocol (PP) population. If any scenarios are expected to cause a difference in endpoint measurements that affects a particular implant more than another, then (at that point) the subject's data should no longer be considered.

Baseline data of the study groups will be compared descriptively. The purpose of presenting these data is to describe homogeneity or heterogeneity of the study population between treatment groups and for subgroups.

All analysis will be performed using validated statistical software packages.

9.2 Effectiveness analysis

A detailed description of the effectiveness analysis can be found in the statistical analysis plan (SAP).

Primary effectiveness analysis

The primary efficacy objective of this study is to confirm safety and performance of SLActive® implants by means of bone level change 12 months after implant loading.

To assess if SLActive® implants have a change in bone level compared to SLA® a repeated measures model may be used. Given the effects of treatment, quadrant, site, subjects, description of implant, time between measurements and possibly other variables (that could

have an effect on the change in bone level over time), a repeated measures analysis should be used to determine if there is any treatment effect.

Secondary effectiveness analysis

The secondary endpoints as listed in Section 3.4.2 will be compared between the treatment groups for the time points recorded (Table 2). Comparisons between the treatment groups will be based on 95% confidence intervals.

Beyond the secondary endpoints in the secondary hypotheses, all stated quantitative secondary endpoints should be analyzed using repeated measures modeling. This will control for any effects expected to be significant. The response and/or explanatory variables may need to be transformed depending on their ability to meet the assumptions of the model.

Through using repeated measures modeling and the randomization scheme proposed we may disregard any specific implant within quadrant randomization and the need to limit measure comparisons between two implants alone. This maintains result integrity by including all information in the analysis. Furthermore, secondary variables that have measures across more than two time-points are analyzed with these methods with no loss in data.

The survival analysis will be carried out over the study implants (study control and study test implant) placed at the surgery visit (V2) and within the ITT population. Implant survival will be analyzed using the Kaplan-Meier Survival estimate with Confidence Intervals (CI) given by the Greenwood formula. Considering that for this study the number of patients not completing the 12 months follow-up visit may exceed 5% due to missed follow-up visits, the formula of Rothman will used for confidence intervals.

Safety and tolerability analysis

The safety analysis will be performed on data collected as specified under 7.3.12 and 7.3.13

The analysis of safety assessments in this study will include summaries of the following of safety and tolerability data collected for each subject:

- Adverse events
- Serious adverse events
- Adverse device effects
- Device deficiencies
- Device deficiencies that could have led to a serious adverse device effect

Summaries of the incidence rates (frequencies and percentages), severity, outcome and relationship to the investigational device and or/ study procedures of individual AEs will be

prepared. AEs which concern an implant position where a BLT, Roxolid® implant was placed during surgery or AEs which are related to a treatment procedure at such a position will be summarized by study treatment and overall and the used products at this position will be listed.

DDs will be summarized per medical device type (implant type, abutment type, instruments).

To address the co-primary objective of this study “SLActive® implants are safe” a descriptive assessment of adverse device effects and device deficiencies that could have led to a serious adverse device effect will be made, this will include listings and tables by treatment, severity, relatedness and outcomes.

9.3 Analysis populations (Data Sets)

The following analysis populations are planned for this study:

Safety Analysis Population (SA)

The safety analysis (SA) population consists of all subjects who were enrolled in the study and who received a study device (BLT, Roxolid® implants).

The SA population will be the basis for the safety analysis.

This population includes the ITT population.

Intent to Treat (ITT) Population

The intent-to-treat (ITT) population consists of each eligible and randomized study subject who received control and test implants in two different quadrants and from whom at least one follow-up measurement after placement is available. This population will include subjects regardless of any protocol deviations (e.g. implant loss of study control or study test implant and/ or premature termination).

The study control and study test implant of the ITT population will be the basis for the implant survival analysis.

Per-Protocol (PP) Population

The per protocol (PP) population consists of each eligible study subject with one study control and one study test implant and who performed all follow-up visits according to the study protocol. Subjects with major protocol deviations (as defined in 11.4.1) will be excluded from this population. In the occurrence of a study control or study test implant loss the patient will be excluded from the PP population. Exclusion of subjects with minor protocol deviations will be determined on a case-by-case basis.

The primary effectiveness analysis will be based on the PP population.

9.4 Sample size

The primary hypothesis is that 12 months after loading, the marginal bone loss around the SLActive® implants will not be appreciably greater than around the SLA® implants.

In the case of MBL, where smaller values are better, the null and alternative hypotheses can be stated as follows:

H_0: Mean MBL for the test >= Mean MBL for the control + tolerance range
H_A: Mean MBL for the test < Mean MBL for the control + tolerance range

The tolerance range or non-inferiority margin characterizes the largest absolute difference which is considered to be dismissible. A MBL of less than 0.5mm within the first year after implant loading constitutes an acceptable clinical standard (28, 45, 46). In this clinical trial, a non-inferiority margin of 20% of the acceptable clinical standard was chosen, which amounts to 0.1mm.

Based on Karabuda et al (28) who compared MBL in SLActive® and SLA® implants one year after loading, if it is assumed that the mean and SD would be 0.46mm ± 0.20mm for SLA® and for the scenario of 0.43mm ± 0.22mm for the SLActive® (with a correlation=0.0), that a difference of 0.10mm or less is unimportant and that the alpha (one tailed) is set to 0.05, then with a sample size of 51 patients (51 pairs, a pair within a patient), the study will have a power of 92.4% to show that the mean MBL for the SLActive® surface is at least as low as the mean for the SLA®. The null hypothesis is then, that the mean for the SLActive® is 0.10 mm higher than the mean for the SLA®, and that the study has a power of 92.4% to reject this null hypothesis.

The Proc Power procedure of the software SAS v9.4, SAS Institute AG, Cary NC USA was used for calculations

60 patients will be enrolled in order to take into account a 20% dropout rate.

10 Obligations of the Principal Investigator

10.1 Investigator Compliance

The Investigators must work according to standard ethical practice as laid down by their professional body and insert the product according to what is described in the handling procedures and the IfU for the products investigated in this clinical study. In addition, they must work in accordance with the “Declaration of Helsinki” (last revision Fortaleza 2013, WMA General Assembly, 2013), the ISO 14155:2011, the European Union’s General Data Protection Regulation (GDPR) and with local legal and regulatory requirements.

The Investigators will ensure that the study is conducted in compliance with this protocol and the Clinical Study Agreement. Specifically, they are responsible for the informed consent process (Section 7.1.1).

11 Study Management

11.1 Insurance

Only CE-marked products within their intended use are investigated. A patient insurance covering the complete duration of the study will be guaranteed by Straumann, if required by local regulations. A copy of the patient insurance will be provided by Straumann and filed in the ISF.

11.2 Site Selection

All study sites were selected by a site qualification assessment where the study design and the study device was presented and the suitability of the sites confirmed (e.g., training and experience of the site staff, appropriate site equipment, access to EC, patient pool and expected recruitment period).

11.3 Regulatory and Ethical Requirements

11.3.1 Informed Consent

Informed consent will be obtained from all patients prior to study participation as described in Section 7.1.1.

Patients who want to withdraw from the study will be offered an alternative treatment related to their dental condition. Patients will be advised of the need for the prescribed follow-up visits for their ongoing care, well-being, and collection of any safety data.

11.3.2 Study Registration

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

11.3.3 Ethics Committee

Prior to initiation of any study procedures, the protocol and informed consent form will be submitted to the local EC of investigators for review and approval before consenting can begin (7.1.1). In addition, any amendments to the protocol or informed consent will be reviewed and approved (if necessary) by the EC. The sponsor must receive a letter documenting the EC approval at the center prior to the initiation and/ or activation of the study. Any additional requirements imposed by the EC shall be followed.

The Investigator and/or Sponsor is responsible for reporting to EC (e.g., annual safety report, SAEs/SADEs, major protocol deviations) as required, during the course of the clinical study.

11.3.4 Patient enrollment

Patient enrollment will only start after the sites have received the site activation letter from the sponsor.

11.3.5 Compliance

This study and any amendments will be performed according to International Organization for Standardization (ISO) 14155:2011 as far as applicable for post-market studies (any deviation will be documented in the internal review check based on Annex A of the ISO), local legal and regulatory requirements, and conform to the Declaration of Helsinki (last revision Fortaleza 2013).

11.3.6 Screening Failures

Any patient that has signed the Informed Consent Form and does not meet eligibility criteria at screening or re-evaluation at surgery is considered a screening failure. In the event of a screening failure, the eCRF should be completed up to the point (in V1 or V2) when the patient was determined to be a screening failure. The Study Termination eCRF page should also be completed. Screening failures will be replaced.

11.4 Protocol Deviations

Protocol deviations are to be avoided. Any deviation from the protocol may jeopardize the study outcome. Non-compliance of the patients, as well as of the Investigators, may lead to the closure of the respective study center.

11.4.1 Definitions

A protocol deviation is any non-compliance with the clinical study protocol, IfU or associated documents. The non-compliance may be on the part of the patient, the Investigator or study staff. Protocol deviations are categorized as:

a) **Major protocol deviation**:

- Increases risk to one or more participants;
- Adversely affects the safety, rights or welfare of one or more participants; or
- Adversely affects the integrity of the study.

Examples of major protocol deviations include: Informed consent obtained after the initiation of study procedures, failure to report a SAE, deviation from inclusion/exclusion criteria, deviation from withdrawal criteria (section 3.7.3), loading of the study control or study test implant not performed at the loading visit

b) **Minor protocol deviation** is a contravention of the protocol that does not impact participant's safety, nor compromises the integrity of the study data, neither/nor ethics of the study. Note: Several minor observations may collectively be considered as equal to a major protocol deviation.

Examples: Delay in performing study procedure (i.e., time window deviation).

Placement of study devices not according to randomization will be discussed on a case by case basis (e.g. assessment from the clinician of the clinical situation in the quadrant where the implants were placed compared to the randomized quadrant).

11.4.2 Procedure

If a protocol deviation has occurred, the following procedure shall be followed:

- All deviations from the protocol must be recorded on the Protocol Deviation eCRF page.
- All **major protocol deviations** that occur at site shall be immediately notified to the sponsor and promptly reported to the local EC according to their requirements (see Section 11.3.3).
- **Minor protocol deviations** shall normally not be reported to the EC, but the sponsor should be notified as part of the study documentation.

Any documentation relating to protocol deviation will be filed in the Investigator Site File.

In case of prospective protocol deviation, the investigator shall notify the sponsor for agreement and submit to the EC for review and approval. The investigator should not implement any deviation from, or changes of, the protocol without agreement from the sponsor, and documented approval/favorable opinion of the EC, if applicable.

11.5 Record Management

11.5.1 Investigator Records

The following will be required from the Investigator prior to the initiation of the study:

- A signed Confidentiality Agreement (or equivalent statement in the Clinical Study Agreement)
- A signed copy of the Clinical Study Agreement with the sponsor
- Signed and dated curriculum vitae of the Investigator(s) and a copy of his/her dental license (if applicable)
- Signed financial disclosure of the Investigator(s), if applicable
- A signed copy of the final protocol and any amendments
- EC approval letter and EC approved informed consent document

11.5.2 Source Documents

Source documents are defined as the original point of entry of a specific data point. Source documents will include, but are not limited to, progress notes, electronic data, computer

printouts, radiographs and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigator and made available for audit or inspection by authorized persons.

The following study specific data can be entered directly into the eCRF in this study:

- Pregnancy test information,
- Review of inclusion and exclusion criteria,
- Selection of quadrants for randomization,
- Pain relief (dose of Paracetamol),
- KM, PPD, BoP, soft tissue (Landry index),
- Final abutment torque,
- Bone level measurements
- Study specific questions in regard to: demographics, medical and dental history, documentation of surgery and documentation of final restoration.

Source data used in this study:

Study specific documentation

- eCRF
- Informed consent process, patient eligibility, study participation (patient files and/or screening and enrollment log)
- Defined study control and test implant (patient files)
- Study termination (patient files)
- Device disposal (implant position and article nr. of products used)
- Osseointegration, inflammation, bacterial load samples and readouts

Routinely collected but at defined study time points

- Patient questionnaire (OHIP-14)
- ISQ readout
- FMPS
- Photographs

Routinely collected data during the daily practice

- Safety data (adverse events, device deficiencies, implant losses, prosthetic complication & failures
- Demographics
- Medical and dental history
- Concomitant medication and procedures
- Documentation of surgery and restoration

- X-rays

11.5.3 Case Report Forms

Required clinical data for this study will be collected using an eCRF for all study patients from whom informed consent is obtained. Center numbers and subject ID will be used to track patient information throughout the conduct of the study.

The Principal Investigator or authorized designee is responsible for the timely and accurate completion of all eCRFs from source documents, query resolution and signature of all eCRFs. The Investigator will also allow Straumann representatives and/or regulatory bodies to review the data reported on the eCRF with the source documents as far as is permitted by local regulations.

11.5.4 Data Management

Data will be collected and recorded using a validated electronic data capturing (EDC) system provided to the centers prior to study start. Automatic queries will be built into the system prior to study start and throughout the project. The site should enter study data into the electronic database within 5 working days of a patient visit. Data capture will be source verified by the monitor and reviewed by the Data Manager. For any missing, inconsistent or illogical data, an electronic query will be generated and sent to the Investigator for completion. The Investigator answers the query, which will be documented.

Once all patients have completed the study, all queries are answered, and data were cleaned by data management, the database will be closed, and the statistical analysis will start.

Patient confidentiality will be strictly maintained.

Details of the data management procedures can be found in the Data Management Plan.

11.5.5 Records/Data Retention

Original radiographs, photographs and study documents will be maintained at the study center in a file established for this study. All study documentation from the site needs to be stored at the study center according to local legal requirements following the completion of the study. 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 for 20 years at Straumann according to Straumann standard operating procedures.

11.6 Patient Retention and Minimizing Loss to Follow-Up

If a patient does not return for any scheduled visits, the Investigator (or designee) will attempt to contact the patient and reschedule the appointment or document the patient's reason for not returning.

If the patient indicates that he/she no longer wishes to be in the study, information will be collected on reason for study withdrawal (e.g., lack of interest, moving, change of dentist, AEs).

11.7 Monitoring

Straumann will assign a qualified CRO or internal personnel to monitor the study. The general monitoring procedures for this study are described below while the details can be found in the Monitoring Plan.

11.7.1 Study Initiation Visit

The Study Manager or 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 and EDC. The study manager or monitor will ensure during the study initiation that the Investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study, including:

- 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 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 EC review and approval of the protocol and informed consent, and to ensure continuing review of the study by the EC.
- Has adequate facilities and access to an adequate number of suitable patients to conduct the study.

Since the study device is long on the market and routinely used by all members of the on site study teams in their daily clinical practice, no device-specific training will be necessary prior to study start.

Our CRO will receive device specific training prior to study start. It will consist in self study of the IFUs and technical information related to the study device.

11.7.2 Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically. Straumann or its delegated monitors will provide clinical monitoring, including review of eCRFs with verification to the source documentation per Monitoring Plan as outlined for the study. 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.

The following will be reviewed during the monitoring visits:

- The study complies with the currently approved protocol/ amendment(s); deviations will be discussed with the responsible Investigator, documented, and reported to the sponsor.
- The study is in compliance with GCP and ISO 14155:2011 and with the applicable regulatory requirements (for details see Section 10.1).
- Only authorized Investigators/ clinical personnel are participating in the clinical investigation.
- Device accountability including adequate supply at site, proper storage and documentation of device traceability.
- The reported study data entered on eCRFs are accurate, complete and verifiable from source documents.
- All AEs (including SAEs) are reported correctly. In cases where there is missing information about an AE or missing evidence to support the Investigator's assessment, the monitor will review and discuss the AE with the responsible Investigator.
- The reason for a patient's withdrawal has been documented.

11.7.3 Study Closeout Visit

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

- Ensure that the documentation and clinical investigation requirements were met.
- Verify that each enrolled subject has a completed and signed eCRF and that all queries are resolved
- Collect outstanding documents.
- Ensure that the current status of all ongoing AE/SAE/DD is documented

- Ensure that all submissions and notifications to the EC were appropriately done according to the EC'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 (see Section 11.5.5).

11.8 Study Termination or Premature Termination

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

The study can be terminated earlier at the discretion of the Investigator or the sponsor in the case of, for example, one of the following:

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

Patients will be advised of the need for follow-up visits for their ongoing care and well-being.

11.8.1 Center Discontinuation

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

- the center is not recruiting a sufficient number of patients or is unlikely to recruit a sufficient number of patients
- the center does not respond to study management requests
- repeated protocol deviations have been discovered that affect the integrity of the study or the study data

11.9 Protocol Amendments

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 Principal

Investigators and the Sponsor have accepted the changes, a written amendment to the protocol will be sent to the Principal Investigators for signature.

EC approval at each study site is required for any significant change in the protocol that may affect the scientific soundness of the study or the rights, safety, or welfare of patients. The change in the protocol may not be implemented until the EC approval is obtained. Each study site will send a copy of the EC approval letter for the amendment to Straumann.

12 Publication Rights

Analysis of data will be conducted by Data Management and the final report will be provided by the sponsor including input from the investigators. The final manuscript will be prepared by the Coordinating Investigator in conjunction with Straumann and submitted for publication. Investigator(s) will be requested to submit their final manuscript to Straumann and will receive comments according to the time frame specified in the Clinical Study Agreement. Additionally, the results of the study will be entered on clinicaltrials.gov.

13 Protocol Signature Page

Study Nr.: CR 2017-05

Study Title: A randomized controlled study to assess intra-patient clinical performance of dental implants with a SLActive® or SLA® surface

Version: Version 2.0; Date: 26 March 2019

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 patients.

Signatures:

Printed Name of Principal Investigator	Signature of Investigator	Date

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15 Appendices

Annex 1: IFU Number 702049: Straumann® Dental Implants: Roxolid® SLActive® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level and Bone Level Tapered (Version D03 09/18)

Annex 2: IFU Number 702107: Straumann® Dental Implants: Roxolid® Standard, Standard Plus, Standard Plus Narrow Neck CrossFit®, Tapered Effect, Bone Level and Bone Level Tapered (Version B01 10/10)

Annex 3: Basic information on the surgical procedures for the Straumann® Bone Level Tapered implant (490.038, Version en/E/00 02/17)

Annex 4: IFU Number 150.923: Straumann® Titanium Abutments and Temporary Abutments/Copings (Version J09 09/18)