A Multi-Center, Prospective, Single Cohort, Post-Market Clinical Follow-Up (PMCF) Study to Assess Implant Survival after Insertion of Straumann® Bone Level Tapered (BLT) Implant Ø 2.9 mm in the Clinical Practice Setting

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Abbreviations

Ø	Diameter
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BLT	Bone Level Tapered
CBCT	Cone-Beam Computed Tomography
eCRF	Electronic Case Report Form
DD	Device Deficiencies
EC	Ethics Committee
EDC	Electronic Data Capturing
FAS	Full Analysis Set
FDI	Federation Dentaire Internationale
GCP	Good Clinical Practice
IfU	Instructions for Use
ISO	International Organization for Standardization
ITI	International Team for Implantology
mSBI	modified Sulcus Bleeding Index
PES	Pink Esthetic Score
PI	Plaque Index
PMCF	Post-Market Clinical Follow-Up
PPS	Per-protocol set
PPD	Probing Pocket Depth

SAS	Safety analysis set
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SLA	Sand blasted, Large grit, Acid etched surface
SC	Small CrossFit
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

Synopsis

Study Title	A Multi-Center, Prospective, Single Cohort, Post-Market Clinical Follow-Up (PMCF) Study to Assess Implant Survival after Insertion of Straumann® Bone Level Tapered (BLT) Implant Ø 2.9 mm in the Clinical Practice Setting
Study Protocol Number	CR 02/15
Study Registration	This protocol will be registered at clinicaltrials.gov at the study start.
Objectives	The aim of this study is to provide short-term data on the performance and safety of the Straumann® BLT implant Ø 2.9 mm in the clinical practice setting. The primary objective of this PMCF study is to assess implant survival at 12 months after implant placement of the Straumann® BLT implant Ø 2.9 mm in usual clinical practice setting in partially healed extraction socket of the central and lateral incisors in the mandible and lateral incisors in the maxilla for single tooth replacement. The secondary objectives of the study are to assess the Pink Esthetic Score (PES) at 6 months after implant placement, the implant success and the marginal bone level changes at 12 months after implant placement, and the incidence of Adverse Events (AEs) and Adverse Device Effects (ADEs).
Design	A multi-center, prospective, single cohort, PMCF study.
Study Population	Male or female patients 18 years of age or older who are in need of a single tooth replacement with a dental implant in central and lateral incisors in the mandible and lateral incisors in the maxilla, and meet all of the inclusion but none of the exclusion criteria listed below.
Patient Inclusion Criteria	The following criteria must be met for inclusion in the study: • Patients must have voluntarily signed the Informed Consent Form before any study related procedures are performed, are willing and able to attend scheduled follow-up visits, and agree that the pseudonymized data will be collected and analyzed. • Patients must be males or females who are a minimum of 18 years of age. • Patients with a minimum of 4 weeks history of edentulism in the study area, minimal interdental space and in need of a single tooth replacement with a dental implant in central and lateral incisors in the mandible and lateral incisors in the maxilla (Federation Dentaire Internationale (FDI) positions 12, 22, 31, 32, 41 or 42). • Presence of natural tooth or implants adjacent to the study implant position (single tooth gap). • Patients with complete soft tissue coverage of the socket at the Baseline Visit.
Patient Exclusion Criteria	Patients matching any contraindication as stated in the Instructions for Use (IfU) should be excluded: • Patients with inadequate bone volume and / or quality. • Patients with local root remnants. • Patients with inadequate wound healing capacity. • Patients with not completed maxillary and mandibular growth.

	• Patients with serious internal medical problems, uncontrolled bleeding disorders, psychoses, prolonged therapy-resistant functional disorders, xerostomia, weakened immune system, illnesses requiring periodic use of steroids or uncontrollable endocrine disorders. • Patients with poor general state of health. • Patients with drug or alcohol abuse. • Patients with allergies or hypersensitivity to chemical ingredients of titanium-zirconium alloy. • Patients with conditions or circumstances, in the opinion of the Investigator, which would prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance or unreliability. • A woman who is pregnant or planning to become pregnant at any point during the study duration.		
Study Treatment	Placement of Straumann® BLT implants Ø 2.9 mm in central and lateral incisors in the mandible and lateral incisors in the maxilla in at least 40 patients for single tooth replacement followed by prosthetic loading (only 1 implant per patient is assessed).		
Treatment Plan	**Visit #**	**Visit**	**Schedule**
	Visit 1	Screening	Up to 2 months before implant placement
	Visit 2	Implant Placement (Baseline)	Day 0
	Visit 3	Suture Removal	7 to 14 days after implant placement
	Visit 4	Provisional Crown	6 weeks ± 2 weeks after implant placement
	Visit 5	Final Crown	4 months ± 1 month after implant placement
	Visit 6	6-month Follow-Up	6 months ± 1 month after implant placement
	Visit 7	12-month Follow-Up	12 months ± 1 month after implant placement
Study Device	Straumann® BLT implant Ø 2.9 mm Roxolid® SLActive®, available in lengths of 10, 12 and 14 mm.		
Registration Status	CE-marking for the Straumann® BLT implant Ø 2.9 mm is expected during the second half year of 2015. The study will not start until CE-clearance has been received.		

Primary Analysis	The analysis will be conducted after all patients completed the 12-month Follow-Up Visit. Baseline is implant placement.
Primary Endpoint	• Implant survival at 12 months after implant placement
Secondary Endpoints	• PES at 6 months after implant placement • Implant success at 12 months after implant placement • Marginal bone level changes at 12 months after implant placement • AEs and ADEs incidence
Statistical Considerations	Descriptive statistics will be performed.
Safety	The patients will be monitored for AEs and ADEs by the Investigators from the start of implant placement at the Baseline Visit until the last protocol-specific procedure of a patient.
Participating Country	Germany
Number of participating centers	5 study centers
Number of Patients	At least 40 patients
Estimated Date of First Patient In / Study Start	October 2015 (after CE-marking)
Estimated Date of Last Patient In	December 2017
Estimated Date of Last Patient Out / Study End	December 2018 (12-month Follow-Up Visit completed by all patients)
Sponsor	Institut Straumann AG
Investigators	Dr. Dr. Keyvan Sagheb (Coordinating Investigator), University Mainz Prof. Dr. Dr. Johannes Kleinheinz, University Münster Priv.-Doz. Dr. Dr. Marcus Klein, Private Practice Stroink, Düsseldorf Jan Herrmann, Private Practice Hentschel & Herrmann, Zwickau Prof. Dr. Dr. Christian Walter, medi+, Mainz
Compliance	This study and any amendments will be performed according to International Organization for Standardization (ISO) 14155:2011 as applicable for post-market studies, ICH E6(R1) Guideline on Good Clinical Practice (GCP) 1996, local legal and regulatory requirements, and conformed to the Declaration of Helsinki (last revision Fortaleza 2013).

Table of Content

1 Background and Study Rationale

In order to improve the safety and success in particular for dental implants with a reduced diameter (Ø), Straumann® developed the material Roxolid®. It is alloyed from 2 of the most biocompatible materials, titanium and zirconium (Steinemann, 2000). Material specifications and dynamic tests have shown improved implant strength (Gottlow et al., 2012 and Kobayashi et al., 1995). Furthermore, it features the fast osseointegrating hydrophilic and chemically active Sand blasted, Large grit, Acid etched SLActive® surface. Animal studies have shown that the SLActive® surface on Roxolid® has comparable osseointegration properties as on pure titanium (Gottlow et al., 2012). Combining higher strength with excellent osseointegration substantially increases implant safety. Clinical performance of the Roxolid® Ø 3.3 mm implant was documented by Al-Nawas et al., 2012, Benic et al., 2013, Al-Nawas et al., 2014 and Quirynen et al., 2015.

Straumann® has developed a novel, 2-piece dental implant based on Roxolid® and SLActive® technology with a diameter of 2.9 mm (Straumann® Bone Level Tapered (BLT) implant Ø 2.9 mm) to allow treatment of patients with single tooth gaps of small dimensions. This implant is indicated for single tooth replacement of the lateral and central incisor positions in the mandible and for the maxillary lateral incisors. These positions are reduced-load-bearing compared to more posterior positions. One of the rationales for the use of the Straumann® BLT implant is the patient's benefit to decrease the rate of augmentations necessary for implant insertion in comparison with standard diameter implants.

According to the 5th International Team for Implantology (ITI) Consensus Conference 2-piece implants with a diameter of 3.0 to 3.25 mm are documented for non-load-bearing single tooth gaps (Klein et al., 2014).

2 Objectives

The aim of this study is to provide short-term data on the performance and safety of the Straumann® BLT implant Ø 2.9 mm in the clinical practice setting.

2.1 Primary Objective

The primary objective of this post-market clinical follow-up (PMCF) study is to assess implant survival at 12 months after implant placement of the Straumann® BLT implant Ø 2.9 mm in the usual clinical practice setting in partially healed extraction socket of the central and lateral incisors in the mandible and lateral incisors in the maxilla for single tooth replacement.

2.2 Secondary Objectives

The secondary objectives of the study are to assess the Pink Esthetic Score (PES) at 6 months after implant placement, the implant success and the marginal bone level changes at 12 months after implant placement, and the incidence of Adverse Events (AEs) and Adverse Device Effects (ADEs).

3 Study Design

3.1 Type and Design of the Study

This is a multi-center, prospective, single cohort, PMCF study.

3.2 Indications and Contra-Indications

Straumann® BLT implants Ø 2.9 mm are suitable for the functional and esthetic oral rehabilitation of single tooth gaps in Federation Dentaire Internationale (FDI) positions 12, 22, 31, 32, 41 or 42. Because of their reduced mechanical stability, Straumann® BLT implants Ø 2.9 mm are only used in cases with low mechanical load. Placement in posterior regions is not recommended. The prosthetic restorations used are single crowns, which are connected to the implants by the corresponding elements (Straumann® Variobase® Small CrossFit® (SC) abutments).
The complete details of the Instructions for Use (IfU) for the Straumann® BLT implant Ø 2.9 mm can be found in the Annex 1.

3.3 Study Treatment

Straumann® BLT implants Ø 2.9 mm will be placed in at least 40 patients (only 1 implant per patient is assessed) within the intended use: central and lateral incisors in the mandible and lateral incisors in the maxilla for single tooth replacement followed by prosthetic loading (see IfU, Annex 1). When placing the implant, the soft tissue coverage of the socket should be complete (Type 2, according to the categorization of Hämmerle et al., 2004), which takes typically 4 to 8 weeks after extraction.

The choice of the implantation procedure and the loading protocol within given time frames (Section 6) is the responsibility of the Investigator. The Investigator will decide on the best treatment plan for the patient within the description provided in the brochure “Basic Information on the Surgical and Prosthetic Procedures for the Straumann® Bone Level Tapered Implants Ø 2.9 mm SC” (Annex 2).

In the brochure “Basic Information on the Surgical and Prosthetic Procedures for the Straumann® Bone Level Tapered Implants Ø 2.9 mm SC” (Annex 2), details about the

necessary bone volume and the spacing between implants and the distance from adjacent teeth can be found.

3.4 Endpoints

3.4.1 Primary Endpoint

The following parameter will be measured as primary endpoint:

- Implant survival at 12 months after implant placement

3.4.2 Secondary Endpoints

The following parameters will be measured as secondary endpoints:

- PES at 6 months after implant placement
- Implant success at 12 months after implant placement
- Marginal bone level changes at 12 months after implant placement
- AEs and ADEs incidence

3.5 Study Sample Size

The study will enroll at least 40 patients at 5 study centers. Two university hospitals and 3 private dental practices in Germany will be involved.

3.6 Study Duration

In October 2015, after CE-marking of the Straumann® BLT implant Ø 2.9 mm, it is expected that the 1st patient will be enrolled in the study. In December 2017, patient recruitment is expected to be complete.

Treatment phase per patient will be approximately 4 months from surgery to placement of the final crown. Each patient will be followed for 12 months after implant placement and data will be collected during this time period. The total duration of the study is expected to span 18 months (2.5 year). Hence, the end of the study is planned to be in December 2018.

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 a single tooth replacement with a dental implant in central and lateral incisors in the mandible and lateral incisors in the maxilla, and meet all of the inclusion (Section 3.7.1) but none of the exclusion criteria (Section 3.7.2).

Patients will be asked to provide informed consent in writing prior to any study related procedures (Section **Error! Reference source not found.**) and will be considered "consented" in the study. This will be documented in the Screening and Enrollment Log. Patients will be evaluated based on the inclusion and exclusion criteria for initial eligibility during the Screening Visit. Patients who provide informed consent and meet the enrollment criteria will be invited to enroll into the study. Once the patient receives the Straumann® BLT implant Ø 2.9 mm, he/she is considered "enrolled" in the study and the second part of the Screening and Enrollment Log will be completed. Patients who are not eligible to receive the Straumann® BLT implant Ø 2.9 mm will be considered "screening failures" (Section 11.3.4).

3.7.1 Inclusion Criteria

For this study, inclusion criteria are particularly broad and exclusion criteria limited in order to document patients' treatment with Straumann® BLT implants Ø 2.9 mm in usual clinical practice.

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

- Patients must have voluntarily signed the Informed Consent Form before any study related procedures are performed, are willing and able to attend scheduled follow-up visits and agree that the pseudonymized data will be collected and analyzed.
- Patients must be males or females who are a minimum of 18 years of age.
- Patients with a minimum of 4 weeks history of edentulism in the study area, minimal interdental space and in need of a single tooth replacement with a dental implant central and lateral incisors in the mandible and lateral incisors in the maxilla (FDI positions 12, 22, 31, 32, 41 or 42).
- Presence of natural tooth or implants adjacent to the study implant position (single tooth gap).
- Patients with complete soft tissue coverage of the socket at the Baseline Visit.

3.7.2 Exclusion Criteria

Patients matching any contraindication as stated in the IfU (Annex 1) should be excluded:

- Patients with inadequate bone volume and / or quality or metabolic bone disorder.
- Patients with local root remnants.
- Patients with inadequate wound healing capacity.
- Patients with not completed maxillary and mandibular growth.

- Patients with serious internal medical problems, uncontrolled bleeding disorders, psychoses, prolonged therapy-resistant functional disorders, xerostomia, weakened immune system, illnesses requiring periodic use of steroids or uncontrollable endocrine disorders.
- Patients with poor general state of health.
- Patients with drug or alcohol abuse.
- Patients with allergies or hypersensitivity to chemical ingredients of titanium-zirconium alloy.
- Patients with conditions or circumstances, in the opinion of the Investigator, which would prevent completion of study participation or interfere with analysis of study results, such as history of non-compliance or unreliability.
- A woman who is pregnant or planning to become pregnant at any point during the study duration.

4 Device Description and Specifications

4.1 Straumann Bone Level Tapered Implant Ø 2.9 mm

The complete details of the product description and instructions for the Straumann® BLT implant Ø 2.9 mm can be found in the “Basic Information on the Surgical and Prosthetic Procedures for the Straumann® Bone Level Tapered Implants Ø 2.9 mm SC” (Annex 2) and in the IfU (Annex 1). The implants are available with a length of 10, 12 and 14 mm. They are designed to be placed at bone level. They are made of a binary titanium-zirconium alloy (commercial name Roxolid®) and feature the SLActive® surface, which is a hydrophilic and chemically acitive large grit sand blasted and acid etched surface. The chemically activated state is preserved by storage in a physiological sodium chloride solution.

The Straumann® BLT implants Ø 2.9 mm listed in Table 1 will be available for use in this study.

The clinician may select the appropriate restorative components for the case from any of the Straumann® restorative components listed in Table 1.

Table 1: Description of the Implants and Abutments

Material	Roxolid®
Surface	SLActive®
Device model image	 Straumann® Bone Level Tapered Implant Ø 2.9 mm
Geometry	Bone Level Tapered
Endosteal diameter	2.9 mm
Internal connection	Small CrossFit® (SC)
Implant lengths	10, 12, 14 mm
Prosthetic restoration components	Straumann® Variobase® SmallCrossFit® SC Abutments

4.2 Product Registration Status

Straumann® BLT implants Ø 2.9 mm and the corresponding prosthetic components are expected to be CE-marked in the second half of 2015 and will only be used within their indications. The study will not start until CE-clearance for all components involved has been received.

4.3 Instructions for Use, Handling and Labeling

Straumann® will provide the 5 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.

The study device must be used as described in the IfU (Annex 1).

Device Deficiencies (DDs) shall be reported to Straumann® on the DD eCRF page as described in Section 8.3.3

4.4 Storage

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

4.5 Device Accountability

The Investigator must maintain an accurate and up-to-date accountability record of all study devices received, used, discarded (opened, but non-used) and returned during the course of the study. This information shall be recorded in the Device Accountability Record Log.

At each monitoring visit, the monitor will check the study device accountability for accuracy and completeness.

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

4.6 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 Analysis, Risk/ Benefits

The device risk analysis and risk assessment for the BLT implants was conducted according to EN International Organization for Standardization (ISO) 14971 for CE-marked implants. Full results are included in the Risk Management Report dated 25 February 2016.

Refer to Table 6 for a list of potential expected ADEs following the insertion of dental implants.

Read carefully the risks associated with the study device and the procedures involved in its use listed in the IfU (Annex 1) under Warning and Cautions/Precautions.

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

Potential benefits of the placement of the Straumann® BLT implant Ø 2.9 mm may include less invasive surgery and reduced need of bone augmentation.

6 Schedule of Assessments

An overview of the study procedures and evaluations is provided in Table 2.

Table 2: Schedule of Assessments

Category	Evaluation	VISIT 1 Screening (Month -2 to Day -1)	VISIT 2 Implant Placement (Baseline) Day 0	VISIT 3 Suture Removal Day 7 to 14	VISIT 4 Provisional Crown 6 w (±2 w)	VISIT 5 Final Crown 4 m (±1 m)	VISIT 6 Follow-up 6 m (±1 m)	VISIT 7 Follow-up 12 m (±1 m)
Consent, demographic and baseline characteristics	Informed consent	X						
	If female, pregnancy test	X						
	Demographics (date of birth, gender, ethnic origin)	X						
	Smoking status	X						
Selection	Patient eligibility	X	X					
Medical/dental history	Medical history	X						
	Dental history / pre-operative planning	X						
Study parameters	Oral hygiene assessment	X	X	X	X	X	X	X
	Plaque Index						X	X
	Modified Sulcus Bleeding Index	X				X	X	X
	Probing Pocket Depth						X	X
	Photograph of the implant site	X	X	X	X	X	X	X
	X-ray	X[1]	X[2]			X[2]		X[2]
	Implant success criteria					X	X	X
	Implant survival			X	X	X	X	X
	Pink esthetic score						X	X
Safety	Adverse events		X	X	X	X	X	X
	Changes in concomitant medication		X	X	X	X	X	X
Treatment	Implant placement		X					
	Suture removal			X				
	Provisional crown				X			
	Final crown					X		

d=day, m=month, w=week.
[1] At screening, this should either be a panoramic radiograph or full mouth Cone-Beam Computed Tomography scan.
[2] At Visits 2, 5 and 7, peri-apical X-rays should be taken.

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 2 months before implant placement
Visit 2	Implant Placement (Baseline)	Day 0
Visit 3	Suture Removal	7 to 14 days after implant placement
Visit 4	Provisional Crown	6 weeks ± 2 weeks after implant placement
Visit 5	Final Crown	4 months ± 1 month after implant placement
Visit 6	6-month Follow-Up	6 months ± 1 month after implant placement
Visit 7	12-month Follow-Up (Primary Endpoint)	12 months ± 1 month after implant placement

6.2 Screening Visit (Visit 1)

At the Screening Visit (up to 2 months before the implant surgery), the Investigator (or designee) will review the study with the patient and invite him/her to participate. Once written informed consent has been obtained, an initial evaluation will be conducted to determine whether the patient meets the study inclusion criteria and not any of the exclusion criteria and specified study information will be collected. The following evaluations will be performed and documented at the Screening Visit, which are described in details 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 **Error! Reference source not found.**
- If female, pregnancy test
- Demographics
- Smoking status
- Patient eligibility (inclusion and exclusion criteria)
- Medical and dental history / pre-operative planning
- Oral hygiene assessment
- Modified Sulcus Bleeding Index (mSBI)
- Photograph of the implant site
- Panoramic radiograph or full mouth Cone-Beam Computed Tomography (CBCT) scan

6.3 Implant Placement (Baseline; Visit 2)

The inclusion and exclusion criteria should be re-evaluated at the Baseline Visit prior to implant placement to confirm eligibility. Straumann® BLT implant Ø 2.9 mm will be placed in accordance to the protocol and recommendations given by the manufacturer (see Section 3.3), and bone augmentation procedures will be performed, if applicable. Primary stability will be assessed by hand testing after implant placement. See Section 7.18 for the required documentation regarding the implant placement.

The following evaluations will be performed and documented at the Baseline Visit, which are described in details in Section 7:

- Review of the patient eligibility (inclusion and exclusion criteria)
- Oral hygiene assessment
- Photographs of the implant site
- X-ray
- AEs
- Changes in concomitant medications
- Details of implant placement

6.4 Suture Removal (Visit 3)

At Visit 3, sutures will be removed according to the routine of the respective study center and Investigator. Usually sutures are removed 7 – 14 days after implant surgery.

The following evaluations will be performed and documented at Visit 3, which are described in details in Section 7:

- Oral hygiene assessment
- Photograph of the implant site
- Implant survival
- AEs
- Changes in concomitant medications
- Suture removal

6.5 Provisional Crown (Visit 4)

At Visit 4, approximately 6 weeks after implant surgery, the gingiva will be re-opened, if applicable, and a provisional crown will be placed according to the routine of the respective

study center and Investigator. See Section 7.19 for the required documentation regarding the placement of the provisional crown.

The following evaluations will be performed and documented at Visit 4, which are described in details in Section 7:

- Oral hygiene assessment
- Photograph of the implant site
- Implant survival
- AEs
- Changes in concomitant medications
- Details of the selected provisional crown

6.6 Final Impression (not a scheduled visit)

The final impression will be taken by the prosthodontist.

6.7 Final Crown (Visit 5)

At Visit 5, approximately 4 months after implant surgery, the final crown will be placed according to the routine of the respective study center and Investigator.

The following evaluations will be performed and documented at Visit 5, which are described in details in Section 7:

- Oral hygiene assessment
- mSBI
- Photograph of the implant site
- X-ray
- Implant success criteria
- Implant survival
- AEs
- Changes in concomitant medications
- Details of the final crown

In case the final crown will be placed by the general dentist, the patient must visit the study center after the final crown was placed within the given time window to perform the evaluations listed above.

6.8 Follow-Up after 6 Months (Visit 6)

The following evaluations will be performed at Visit 6, which are described in details in Section 7:

- Oral hygiene assessment
- Plaque Index (PI)
- mSBI
- Probing Pocket Depth (PPD)
- Photograph of the implant site
- Implant success criteria
- Implant survival
- PES
- AEs
- Changes in concomitant medications

6.9 Follow-Up after 12 Months (Visit 7)

The following evaluations will be performed at Visit 7, which are described in details in Section 7:

- Oral hygiene assessment
- PI
- mSBI
- PPD
- Photograph of the implant site
- X-ray
- Implant success criteria
- Implant survival
- PES
- AEs
- Changes in concomitant medications

7 Study Evaluations

7.1 Informed Consent

It is the responsibility of the Investigator, or an authorized person designated by the Investigator to obtain informed consent in writing from each patient participating in this study prior to any study related procedures. As part of the informed consent discussion, the Investigator must provide an adequate explanation of the overall requirements/procedures of the study, purpose of the study, the nature of the planned treatment, any alternative procedures, and possible risks, complications, or benefits of the study. The Investigator or designee must also explain that the 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 must be provided for the patient to read and understand the Informed Consent Form and to consider participation in the clinical investigation. Patients must read, understand and sign 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 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)) 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 a screening failure (see Section 11.3.4).

7.2 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. The test result must be documented in the source data. A woman who

is pregnant or planning to become pregnant at any point during the study duration cannot be enrolled in this study.

If a woman becomes pregnant during the study, an AE form should be completed. The woman should be followed for the duration of the pregnancy, without the study required peri-apical radiographs, and the outcome of the pregnancy should be documented (Section 8.5).

7.3 Demographics

Patient demographics (date of birth, gender and ethnic origin) need to be documented at screening (Table 2).

7.4 Smoking Status

Smoking status need to be documented at screening (Table 2). It will be assessed if patients are current or past smokers and they will be classified into:

- Non-smokers
- Light smokers: 1 to ≤ 10 cigarettes per day
- Heavy smokers: > 10 cigarettes per day

7.5 Inclusion and Exclusion Criteria

At screening, the inclusion and exclusion criteria will be evaluated according to Sections 3.7.1 and 3.7.2, and will be re-evaluated at baseline. Patients must fulfill all of the inclusion criteria and must not meet any of the exclusion criteria to be eligible for enrollment in the study.

7.6 Medical and Dental History / Pre-Operative Planning

Medical and dental history / pre-operative planning will be obtained at the Screening Visit (Table 2). Relevant medical history (e.g., systemic diseases) and current medical conditions will be evaluated by the Investigator based on the information available. The information may be obtained from the patient's general physician or from oral communication with the patient. Dental history / pre-operative planning should include position of the missing tooth, description of tooth loss, description of the adjacent dentition, prosthetic history and details of bone augmentation procedures if applicable.

7.7 Oral Hygiene Assessment

The patient's overall oral hygiene will be evaluated at each study visit (Table 2) starting with the Screening Visit by choosing one of the following: "excellent", "good", "fair" or "poor".

7.8 Plaque Index

Plaque Index will be assessed at the time points listed in the schedule of assessment (Table 2).

It will be evaluated on the mesial, buccal, distal and palatal surfaces of the implant site using the four-point scale PI developed by Silness and Loe (Silness and Loe 1964):

- Score 0 – no plaque.
- Score 1 – a film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface.
- Score 2 – moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye.
- Score 3 – abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

7.9 Modified Sulcus Bleeding Index

Modified Sulcus Bleeding Index will be assessed at the time points listed in the schedule of assessment (Table 2).

It will be documented if bleeding is induced at the marginal gingival tissue by running a blunt periodontal probe along the soft tissue wall at the orifice of the pocket. The bleeding tendency will be evaluated on the implant site at 4 locations (mesial, buccal, distal, palatal) and assessed using the mSBI by Mombelli (Mombelli et al. 1987):

- Score 0 – no bleeding when a periodontal probe is passed along the gingival margin.
- Score 1 – isolated bleeding spot visible.
- Score 2 – blood forms a confluent red line on margin.
- Score 3 – heavy or profuse bleeding.

7.10 Probing Pocket Depth

Probing Pocket Depth will be assessed at the time points listed in the schedule of assessment (Table 2).

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

7.11 Photograph of the implant site

Digital intra-oral photographs should be taken at each study visit (Table 2):

- Visit 1
- Visit 2:
    - After surgical flap
    - After implant bed preparation
    - After implant insertion (photograph should include augmentation, if applicable)
    - When surgery is completed
- Visit 3
- Visit 4:
    - Before re-opening
    - After re-opening
- Visit 5:
    - Before insertion of the final crown (after the provisional one was removed)
    - After insertion of the final crown
- Visit 6
- Visit 7

7.12 Panoramic Radiograph or Cone-Beam Computed Tomography Scan

A panoramic radiograph or full mouth CBCT scan must be available at the Screening Visit to assess the complete dentition and to use in surgical planning. The screening panoramic radiograph or full mouth CBCT scan can be taken during the Screening Visit or be available from a previous date within 6 months of the implant surgery (Table 2).

7.12.1 Bone Level Changes

Peri-apical X-rays are standard procedures during implant surgery to assess changes of the bone level. Peri-apical X-rays will be taken at baseline (Visit 2), at placement of the final crown (Visit 5) and at the end of the study (Visit 7) to assess bone level changes between implant placement (Baseline Visit) and placement of the final crown (Visit 5) as well as between implant placement and the 12-month Follow-Up Visit (Visit 7) (Table 2).

An independent expert will be contracted to perform the bone level measurements from the X-rays. The vertical bone level will be evaluated by measuring the distance from the implant shoulder to the first visible bone contact on the implant. Measurements will be taken at the mesial and distal aspects of the implant, and an average value will be calculated. Mean bone level changes will be computed by subtracting the average bone level at Visit 5 from the average bone level at baseline (implant placement) and by subtracting the average bone level at the 12-month Follow-Up Visit (Visit 7) from the average bone level at baseline (implant placement). Hence, negative bone level changes are representing bone loss between baseline and Visit 5 and between baseline and the 12-month Follow-Up Visit, respectively; vice versa positive changes representing bone gain. Measurements will take into account distortion based on changes on the radiograph from the true dimension of the implant.

7.13 Implant Success Criteria

Implant success will be assessed at the time points listed in the schedule of assessment (Table 2).

A **"successful implant"** is an implant where all of the following success criteria (according to Buser et al., 1990) apply:

1. Absence of persisting subjective discomfort such as pain, foreign body perception and/or dysesthesia (painful sensation);
2. Absence of recurrent peri-implant infection with suppuration;
3. Absence of tactile implant mobility;
4. Absence of a continuous peri-implant radiolucency.

Failed implants will be counted as not successful.

7.14 Implant Survival

Implant survival will be assessed at the time points listed in the schedule of assessment (Table 2).

A **"surviving implant"** is an implant stably inserted in the jaw. Note, that a surviving implant may not be successful if the success criteria (see Section 7.13) are not fulfilled.

A **"failed implant"** is an implant that:

- Has been removed; or
- Has fractured beyond repair.

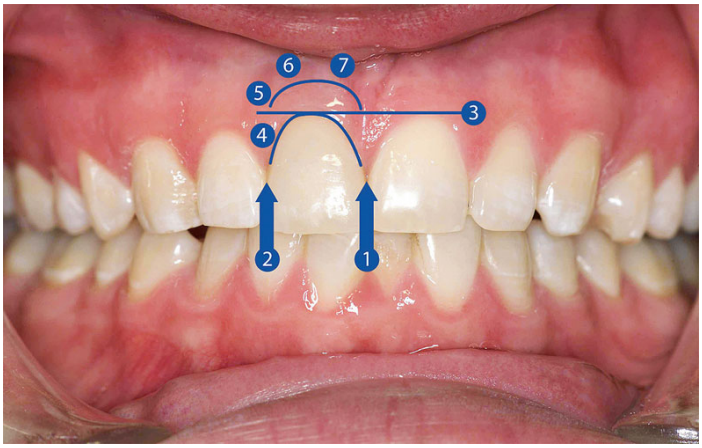
7.15 Pink Esthetic Score

PES will be assessed by the Investigator at the time points listed in the schedule of assessment (Table 2). The PES score allows an objective evaluation of peri-implant soft tissue of single tooth implants based on 7 parameters (Table 4 and Figure 1) and is highly reproducible. Each variable will be assessed using a 0-1-2 scoring system; 0 being the lowest, and 2 being the highest value. The maximum achievable PES is 14 (Fürhauser et al., 2005).

Table 4: Pink Esthetic Score Variables

	Score		
Variablen	**0**	**1**	**2**
Variables			
(1) mesiale Papille	fehlt	unvollständig	vollständig
(1) mesial papilla	*missing*	*incomplete*	*complete*
(2) distale Papille	fehlt	unvollständig	vollständig
(2) distal papilla	*missing*	*incomplete*	*complete*
(3) Weichgewebe-Kontur	unnatürlich	fast natürlich	natürlich
(3) soft tissue contours	*unnatural*	*virtually natural*	*natural*
(4) Weichgewebe-Level	Diskrepanz > 2 mm	Diskrepanz 1–2mm	Diskrepanz < 1 mm
(4) soft tissue level	*discrepancy > 2 mm*	*discrepancy 1–2mm*	*discrepancy < 1 mm*
(5) Alveolarfortsatz	deutlich vermindert	leicht vermindert	Kein Unterschied
(5) aleveolar process	*clearly resorbed*	*slightly resorbed*	*no difference*
(6) Weichgewebe-Farbe	deutlicher Unterschied	leichter Unterschied	kein Unterschied
(6) soft tissue coloring	*clear difference*	*slight difference*	*no difference*
(7) Weichgewebe-Textur	deutlicher Unterschied	leichter Unterschied	kein Unterschied
(7) soft tissue texture	*clear difference*	*slight difference*	*no difference*

Figure 1: Visualization of the Pink Esthetic Score Variables



Refer to Table 4 for description of the variables.

7.16 Adverse Events

At each visit the Investigator should determine if any AEs occurred since the last study visit by speaking with the patient and reviewing any dental and medical records. These AEs, along with any AEs from the current study visit, should be documented 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 8.4.

7.17 Concomitant Medication

Concomitant medication, procedures and supportive therapies will be recorded at the Screening Visit. Any changes in the concomitant medications, procedures and supportive therapies must be documented at each study visit until the end of the study. Prophylactic antibiotics and anesthesia given do not need to be recorded on the Concomitant Medication eCRF page as long as they are taken by the patients in the same or lower dosage as during standard treatment during the following procedures:

- Visit 2: Implant placement
- Visit 3: Suture removal
- Visit 4: Placing of the provisional crown
- Visit 5: Placing of the final crown.

7.18 Details of Implant Placement

At the Baseline Visit, the implant placement procedure needs to be documented as follows (Table 2):

- Time since tooth was lost or removed (note, soft tissue coverage of the socket should be complete at baseline; i.e., Type 2 according to the categorization of Hämmerle et al., 2004);
- Type of healing procedure (subgingival or transgingival) and if soft tissue transplant was required;
- Bone quality according to the 4 different bone types described by Lekholm et al., 1985;
- Implant length;
- Details of the surgery (including site of implant placed);
- Details of augmentation procedures (e.g., bone graft used);
- Torque measurements if applicable;

- Stability of the implant after placement. The implant can be considered as primary stable or instable.

7.19 Provisional Crown Description

Details of the selected provisional need to be documented at Visit 4 (Table 2):

- Material of the provisional crown;
- If the provisional crown was loaded in occlusion,
- If soft tissue graft was used.

7.20 Final Crown Description

Details of the final crown need to be documented at Visit 5 (Table 2):

- Material of the final crown;
- If the final abutment was torqued to 35 Ncm with no rotational movement of the implant.

8 Evaluation of Adverse Events and Device Deficiency

8.1 Definition

A summary of the classification for AEs is provided in Table 5.

Table 5: Summary of the Classification for Adverse Events

<table>
<tr><th>Adverse events</th><th>Non-device related</th><th colspan="2">Device or procedure related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="2">Serious</td><td rowspan="2">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated

Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated
Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

8.1.1 Adverse Event

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 study device. This definition includes events related to the study device, or events related to the procedures involved. For users or other persons, this

definition is restricted to events related to study devices. Disease signs and symptoms already existing prior to the use of the study devices are not considered as AE unless they re-occur after the patient has recovered from the preexisting condition, or represent an exacerbation in intensity or frequency.

8.1.2 Serious Adverse Event

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).

This includes DDs that might have led to an SAE if

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

These are handled under the SAE reporting system.

8.1.3 Device Deficiency

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.

Device Deficiencies can be classified into:

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

A DD does not always lead to an AE. In addition, only DDs related to the study device need to be tracked by Clinical Research Team.

8.1.4 Adverse Device Effect

An ADE is an AE related to the use of a study device or procedure (e.g., surgery). This definition includes AEs resulting from insufficient or inadequate IfU, deployment, implantation, installation, or operation, or any malfunction of the study device. This definition includes any event resulting from use error or from intentional misuse of the study device. Any AE which the Investigator believes has even a possible relationship to the device will be classified as an ADE.

8.1.5 Serious Adverse Device Effect

A SADE is an ADE that has resulted in any of the consequences characteristic of a SAE (see Section 8.1.2).

8.1.6 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (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 or IfU (Annex 1).

8.1.7 Anticipated Serious Adverse Device Effect

An Anticipated Serious Adverse Device Effect (ASADE) is an SADE which by its nature, incidence, severity or outcome has been identified in the Risk Management Report or IfU (Annex 1).

8.2 Assessment of Adverse Events

If an AE occurs, the Investigator or another suitably qualified clinician who is trained in recording and reporting AEs and have been delegated to this role (such delegation must be captured in the Study Site Delegation Log) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event.

Each AE should be assessed by the Investigator for seriousness, relationship to the study device or the procedure, severity, expectedness and outcome as described in Sections 8.2.1 to 8.2.5. The rationale for each assessment must be described as well in a short paragraph and source documents should support the designation. To do so, the Investigator reviews systematically all available documentation (e.g., hospital notes, X-rays, laboratory and diagnostic reports) relevant to the event and investigates its cause.

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 Study Device or Procedure

It is useful to analyze an AE in accordance with the time of its occurrence and the surgery date (i.e., during the implantation period of the device, application, or attempt of placement).

8.2.2.1 Relationship to the Study Device

The Investigator will make an assessment of whether the AE is likely to be related to the device according to the following definitions:

- **Definitely Related** – there is a reasonable causal and temporal relationship between the study device and the AE.
- **Possibly Related** – the nature of the event or temporal relationship make it possible that the AE has a causal relationship to the device.
- **Not Related** – no obvious relationship between the study device and the AE.

8.2.2.2 Relationship to the Procedure

The Investigator should assess the relationship of the AE to the implant procedure (e.g., placement of dental implant). The relationship should be assessed using the categories described in Section 8.2.2.1.

8.2.3 Severity

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

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

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.

8.2.4 Expectedness

If the AE is judged to be related to the study device or procedure, i.e., is an ADE, the Investigator will make an assessment of expectedness, or anticipation, based on knowledge of the reaction and any relevant product information as documented in the IfU (Annex 1) or in the

list of potential expected ADEs in the current protocol (Table 6) following the insertion of dental implants. The event will be classed as either:

- **Expected** – the reaction is consistent with the effects of the device listed in the IfU (Annex 1) or list of potential expected ADEs in the current protocol (Table 6) following the insertion of dental implants.
- **Unexpected** – the reaction is not consistent with the effects listed in the IfU (Annex 1) or list of potential expected ADEs in the current protocol (Table 6) following the insertion of dental implants.

Table 6: List of Potential Expected Adverse Device Effects Following the Insertion of Dental Implants

Biological complications

Peri-implant mucositis

- Bleeding (bleeding on probing)
- Bruising
- Mucosal/gingival inflammation (=gingivitis/mucositis, inflammation of the gum tissue)/redness
- Gingival enlargement (=gingival hyperplasia, gingival hypertrophy, gum overgrowth, hypertrophic gingivitis)
- Gingival recession (=dehiscence of the gingiva, receding gums)
- Pain (discomfort)
- Suppuration
- Swelling

Peri-implantitis

- Bleeding (bleeding on probing)
- Bone loss around implant (=peri-implant bone loss)
- Bruising
- Infection at implant site without suppuration
- Infection at implant site with suppuration (=peri-implant abscess)
- Systemic infection
- Pain
- Swelling

Bone integration deficiency

- No primary stability (at surgery)
- Implant mobility (tactile horizontal or vertical)
- Early loss/failure of implant (i.e. before osseointegration) (=primary implant failure)
- Late loss/failure of implant (i.e. after osseointegration) (=secondary implant failure)
- Radiolucency
- Aspiration of implant
- Swallowing of implant

Non-plaque related

- Foreign body sensation
- Material allergy
- Oro-sinus or oro-nasal intrusion/fistula
- Permanent paresthesia/dysesthesia
- Temporary or permanent nerve damage in the jaw

Mechanical complications

- Loosening of abutment or prosthetic screw
- Loosening of an healing cap
- Loss/failure of an abutment
- Loss/failure of an healing cap
- Fracture of abutment or prosthetic screw
- Fracture of implant

Technical complications

- Fracture of prosthesis or veneer
- Irreversible damage to adjacent/opposing teeth
- Loss of cement retention of prosthesis

Other complications

- Esthetic problem
- Aspiration of component(s) (other than implant)
- Jaw, bone fracture
- Phonetic difficulties
- Swallowing of component(s) (other than implant)
- Hypersensitivity (adjacent teeth)

8.2.5 Outcome

The outcome should reflect the status of the AE at the moment of recording.

- **Resolved without Sequelae** – the patient fully recovered from the event without any sequelae. This option also applies when it is unknown whether there are sequelae.
- **Resolved with Sequelae** – the patient'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 patient 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 event increased.

- **Fatal** – the event is related to a death; whether it caused death or contributed to it. If the patient died of a different cause, prior to resolution of the event, the outcome of this event should designated “ongoing”, and not “fatal”, and an end date should not be specified.
- **Unknown** – knowledge of the current status of the event is truly not available to the Investigator (i.e., event was ongoing at last observation, but no further contact with the patient could be established). However, all efforts should be made to determine the outcome of any event, especially that of an SAE/SADE.

8.3 Procedure for Reporting Adverse Events and Device Deficiencies

Adverse Event reporting will begin at the start of implant placement at the Baseline Visit until the last protocol-specific procedure of a patient. All AE/SAEs should be collected, fully investigated and documented in the source document and appropriate eCRF pages for all patients. In the eCRF, only 1 AE/SAE eCRF entry should be completed per event. To ensure patient confidentiality, the reports in Sections 8.3.1 to 8.3.6 will include the patient number only.

The report sequence “initial” shall be ticked on the eCRF page for the initial AE report. In order to capture the new information, the AE eCRF page shall be updated and the report sequence “follow-up” or “final” shall be ticked as appropriate.

Adverse Events like swelling, pain or bleeding do not need to be captured on the eCRF page as long as they occur in the same or milder intensity as during standard treatment during the following procedures:

- Visit 2: implant placement
- Visit 3: suture removal
- Visit 4: Placing of the provisional crown
- Visit 5: Placing of the final crown

8.3.1 Adverse Event Reporting

In the occurrence of an AE, the AE eCRF page should be completed in a timely manner. Safety reporting to the local EC should occur according to the requirements of the EC (see Section 11.3.3).

8.3.2 Serious Adverse Event Reporting

In the occurrence of a SAE, expedited reporting requirements are followed. The AE eCRF page should be completed within 24 h of awareness of the event. The Investigator needs to follow-up on all ongoing SAEs until resolution. In case of a break-down of the eCRF system,

an SAE/SADE Report Form needs to be completed for each event and sent to the sponsor within 24 h of awareness of the event:

Contact address:

Clinical Research, Institut Straumann AG
Phone: +41 61 965 11 11
Fax: +41 61 965 11 10
Email: ClinicalResearch@straumann.com

Safety reporting to the local EC should occur according to the local requirements (see Section 11.3.3).

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

8.3.3 Device Deficiency Reporting

In the occurrence of a DD, the DD eCRF page should be completed in a timely manner. When a DD leads to a potential AE (e.g., bleeding, pain, swelling, infection, peri-implantitis) the AE eCRF page needs to be completed in a timely manner as well. Moreover, DD with SADE potential (e.g., nerve encroachment, sinus perforation, etc.) must be recorded on the AE eCRF page, follow the expedited reporting requirements (within 24 h) and the Investigator needs to follow-up until resolution. In case of a break-down of the eCRF system, an SAE/SADE Report Form needs to be completed for each event and sent to the sponsor within 24 h of awareness of the event:

Contact address:

Clinical Research, Institut Straumann AG
Phone: +41 61 965 11 11
Fax: +41 61 965 11 10
Email: ClinicalResearch@straumann.com

8.3.4 Adverse Device Effects Reporting

Adverse Device Effects must be recorded by completing the AE eCRF page in a timely manner. The Investigator needs to follow-up on all ongoing ADEs until resolution. Safety reporting to the EC should occur according to the local requirements (see Section 11.3.3).

Continuous substantial reduction of the peri-implant bone level is a sign of failure of the implant system. The 1st European Workshop on Periodontology specified an average marginal

bone loss of less than 1.5 mm bone loss within the 1st year after the insertion of the prosthesis, and thereafter less than 0.2 mm annual bone loss as criteria for measuring success (Albrektsson et al., 1993). This has been a standard and a basis for success criteria since it was defined in 1993. In a more recent meta-analysis, the authors looked at Straumann implants and determined that a pooled weighted mean of marginal bone level change for Straumann implants was -0.56 mm (95% CI -0.661 to -0.481) after 5 years. The individual study means of marginal bone level change ranged from -1.0 to -0.15 mm after 5 years (Laurell L et al., 2011). Based on this information the central radiologist will flag any bone level changes that are greater than 2.0 mm in the 1st year after insertion of the prosthesis.

8.3.5 Serious Adverse Device Effect Reporting

In the occurrence of a SADE, expedited reporting requirements are followed. The AE eCRF page should be completed within 24 h of awareness of the event. The Investigator needs to follow-up on all ongoing SADEs until resolution. In case of a break-down of the eCRF system, an SAE/SADE Report Form needs to be completed for each event and sent to the sponsor within 24 h of awareness of the event:

Contact address:

Clinical Research, Institut Straumann AG
Phone: +41 61 965 11 11
Fax: +41 61 965 11 10
Email: ClinicalResearch@straumann.com

The product safety officer at Straumann will work with the Investigator to determine whether the event is anticipated (ASADE) or unanticipated (USADE). In case of USADE, the Investigator must promptly notify its reviewing EC as soon as possible, but no later than 10 working days after 1st learning of the event.

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

8.3.6 Additional Safety Reporting

Straumann will report additional safety information to the centers that is relevant to the protocol or study device and may affect the risk/benefit ratio, the rights, safety or welfare of patients, or the integrity of the study. Such reports may include notification of any changes to the IfU (Annex 1), any publications or interim reports, or any product recalls.

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 patient 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

A qualified statistician will perform all statistical analyses.

Since the purpose of this study is descriptive, there are no formal sample size calculations based on comparative hypothesis testing. Statistical analyses will be descriptive (e.g., reporting means, standard deviations, medians, minima, and maxima for continuous variables and patient counts, frequencies and percentages for categorical variables).

The primary analysis will be conducted after all patients completed the 12-month Follow-Up Visit. Baseline is implant placement.

9.1 Analysis populations (Data Sets)

The following analysis sets are planned for this study:

9.1.1 Safety Data Set

The safety analysis set (SAS) consists of all patients in the study, who received the study implant. The SAS population will be the basis for the safety analysis.

9.1.2 Full analysis set

The full analysis set (FAS) consists of all patients in the study, who received the study implant and from whom at least one follow-up measurement after baseline is available. This analysis will include patients regardless of any protocol deviations and/or premature termination. The primary analysis will be performed by the intent-to-treat principle with the FAS.

9.1.3 Per-Protocol set

The per-protocol set (PPS) consists of all patients in the study, who received the study implant according to the study protocol, completed the study (Visit 1 to Visit 7) and the measurements of the primary variable is available. Patients with major protocol deviations (e.g. deviations from inclusion/exclusion criteria) will be excluded from this population. The primary and secondary analyses will be performed with the PPS as supportive analysis.

9.2 Missing Data

Every effort will be made to minimize the amount of missing data. If a patient drops out of the study prior to completing his/her primary endpoint assessment, the Investigator (or designee) will attempt to call the patient and to collect the information as detailed in Section 11.5.

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, Good Clinical Practice (GCP) and with local legal and regulatory requirements.

The Investigators will ensure that the study is conducted in compliance with this protocol and the Clinical Study Agreement. Specifically, they are also responsible of conducting the informed consent process (Section **Error! Reference source not found.**).

11 Study Management

11.1 Insurance

As only CE-marked products are investigated, the product liability insurance applies.

11.2 Site Selection

The sites were selected by assessing e.g., training and experience of the site staff, site equipment, 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 **Error! Reference source not found.**.

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 will be submitted to the EC at each site for review and approval. 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 of the study at the center. The study will not begin until the required approval from the EC has been obtained. Any additional requirements imposed by the EC shall be followed.

The Investigator is responsible for providing the appropriate reports to the EC during the course of the clinical study. This will include the following:

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

11.3.4 Screening Failures

Any patient that has signed the Informed Consent Form and does not receive the study device is considered a screening failure. In the event of a screening failure, the eCRF page should be completed up to the visit when the patient was determined to be a screening failure. The Study Termination eCRF page should also be completed.

11.3.5 Early Withdrawal

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 and well-being.

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.

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

- Implant loss

The patient withdrawal will be documented on a Study Termination eCRF page and must include the reason for the patient withdrawal. Withdrawn patients will not be replaced and cannot be re-enrolled.

11.3.6 Protocol Deviations

Protocol deviations are to be avoided. Any deviation from the protocol (including deviations from the expected study visit windows) 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.

11.3.6.1 Definitions

A protocol deviation is any non-compliance with the clinical study protocol, GCP, or Manual of Procedures (e.g., the brochure "Basic Information on the Surgical and Prosthetic Procedures for the Straumann® Bone Level Tapered Implants Ø 2.9 mm SC" (Annex 2)) requirements. 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** that in the Investigator's judgment:

- 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, omitting study procedure(s) required by approved protocol, failure to report a SAE, enrolling participants outside of inclusion criteria.

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.

Example: Insignificant delay in performing study procedure (i.e., minor window deviation).

11.3.6.2 Procedure

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

- Recording:
  - All major deviations from the protocol must be recorded on the Protocol Deviation eCRF page.
- Reporting:
  - 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.

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

In case of prospective protocol deviation, the Protocol Waiver/Exception Request Form shall be completed by the Investigator and submitted to the sponsor for agreement and 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/favourable opinion of the EC, if relevant.

11.4 Record Management

11.4.1 Investigator Records

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

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

11.4.2 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.

11.4.3 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. Site numbers and patient numbers will be used to track patient information throughout the registry.

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 a Straumann representative and/or regulatory bodies to review the data reported on the eCRF with the source documents as far as is permitted by local regulations.

11.4.4 Data Management

Data will be collected through an 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 will enter study data into the electronic database as soon as possible after the patient visit. Data capture will be source verified by the monitor and reviewed by the Data Manager. For any missing, out of range or questionable 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 and all queries are answered, the database will be frozen 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.

11.4.5 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 for a period according to the applicable local regulatory and legal requirements after the completion of the study, as specified by the sponsor. The Investigator should have access to the study documents in order to answer any queries associated with the study. All other study records will be kept by Straumann once the study has been completed. These records will be maintained for 20 years at Straumann according to Straumann's Standard Operating Procedures (SOP).

11.5 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 call the patient and reschedule the office appointment or document the patient's reason for not returning.

During the phone call, 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, switching of dentist, AEs).

11.6 Monitoring

Straumann will assign a qualified individual to monitor the study.

11.6.1 Study Initiation Visit

Once a site receives EC approval, Straumann's representative 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. Straumann's representative will ensure during the study initiation that the Investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study:

- Understands the clinical protocol and relevant items outlined in the protocol (including inclusion/exclusion criteria, AE and SAE reporting requirements).

- Understands and accepts the obligations to obtain informed consent.
- Understands how to document study data (especially the importance of having supporting documentation for AE assessment).
- Understands the information outlined in the IfU (Annex 1), including proper device usage.
- Understands aspects of study device accountability (i.e., how to obtain the device, how to store the device, how to document device receipt, usage and return).
- Understands and accepts the obligation to obtain 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.

11.6.2 Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically. Straumann or its delegates monitors will provide clinical monitoring, including review of eCRFs with verification to the source documentation per the Monitoring Plan 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 every monitoring visit:

- The study is in compliance with the currently approved protocol/ amendment(s); deviations will be discussed with the responsible Investigator, documented, and reported to the sponsor.
- 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 center, 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, a monitor will review and discuss the AE with the responsible Investigator.

- The reason for a patient's withdrawal has been documented.

11.6.3 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. The following tasks should be completed by Straumann's representative or the monitor:

- Ensure that the documentation and clinical investigation requirements were met.
- Collect outstanding documents.
- Ensure that AEs were reported to the EC 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 11.4.5).

11.7 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 any 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.

11.7.1 Center Discontinuation

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

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

11.8 Protocol Amendments

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

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

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

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

12 Publication Rights

The Coordinating Investigator will be the corresponding author of a scientific publication. Analysis of data will be done by the data management. The final manuscript will be prepared by the Coordinating Investigator in conjunction with the Institut Straumann AG. The University Mainz reserves the right to comment upon any additional manuscripts intended for publication or public presentation which encompass information obtained during clinical studies supported by the company. Investigator(s) will be requested to submit their final manuscript to Straumann and will receive comments from the company according to the time frame specified in the Clinical Study Agreement.

13 Protocol Signature Page

Center Number:

Protocol: Clinical Study number CR 02/15

Study Title: A Multi-Center, Prospective, Single Cohort, Post-Market Clinical Follow-Up (PMCF) Study to Assess Implant Survival after Insertion of Straumann® Bone Level Tapered (BLT) Implant Ø 2.9 mm in the Clinical Practice Setting

Version: Version 2.0; Date: 09-Aug-2017

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 Study Investigator	Signature	Date

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