Study Code	C-AN-14-001
Date	5 MAR 2015
Version No.	Final V1.00
Investigational Product(s)	ANKYLOS 6.6 mm implant
Sponsor	DENTSPLY IH AB
Address	Aminogatan 1, SE-431 21 Mölndal, Sweden
Phone	+46 31 376 35 00
Fax	+46 31 376 42 10
E-mail address	anna.rydberg@dentsply.com

STUDY TITLE

Implant-fixed restorations with short implants in the edentulous maxilla – A Clinical Investigation over a 5-year follow-up period

The following substantial and non-substantial amendment(s) have been made to this CIP since the date of preparation:

Substantial Amendment No.	**Date of substantial Amendment** *(DD/MMM/YYYY)*	**Local substantial Amendment No.**	**Date of local substantial Amendment** *(DD/MMM/YYYY)*
Non-substantial Amendment No.	**Date of non-substantial Amendment** *(DD/MMM/YYYY)*	**Local non-substantial Amendment no.**	**Date of local non-substantial Amendment** *(DD/MMM/YYYY)*

CLINICAL INVESTIGATION PLAN SYNOPSIS

Study title

Implant-fixed restorations with short implants in the edentulous maxilla – A Clinical Investigation over a 5-year follow-up period

Sponsor

DENTSPLY IH AB d.b.a. DENTSPLY Implants
Aminogatan 1
SE-431 21 Mölndal
Sweden

International Co-ordinating Investigator

Dr. Paul Weigl, Faculty of Oral and Dental Medicine at J.W. Goethe-University Frankfurt am Main, Frankfurt am Main, Germany

Study site(s) and number of subjects planned

Anticipated Number of study sites:	3-4
Anticipated Number of implant treated Subjects	56

Study period

Anticipated First Patient In (FPI)	MAY/2015
Anticipated Last Patient In (LPI)	NOV/2016
Anticipated Last Patient Out (LPO)	MAY/2022

Indication

ANKYLOS® C/X 6.6 mm implants are intended for replacing missing teeth and for supporting single tooth restorations, bridges and prostheses (overdentures).

Investigational Products

ANKYLOS® C/X Implant A 6.6

Objective(s)

Primary objective

The primary objective is implant survival.

Study design

Prospective, multi-center, single-arm study, including a virtual comparison between the 6.6 and 8 mm implant using the SIMPLANT® software system for 3D planning. Subjects will receive 6× 6.6 mm implants in the maxilla. After 3 months of submerged healing, abutments will be installed and implants restored with fixed ATLANTIS™ ISUS bridges. The subjects will be followed up for 5 years.

Subject population

Subjects with totally edentulous maxillas, with natural dentition or fully restored mandibles.

Inclusion criteria

For inclusion in the study subjects must meet all of the following criteria:

1. Aged 18-80 years at inclusion
2. Signed informed consent
3. In need of full-arch restoration of the maxilla

The following should be considered at inclusion but need to be fulfilled at Implant Placement (Visit 3):

4. Maxilla: totally edentulous, fulfilling all of the following criteria:
    a) History of edentulism: ≥ 6 months and
    b) Minimum bone height: ≥ 7 mm and
    c) Minimum bone width: ≥ 5.5 mm

5. Mandible: antagonistic natural dentition or tooth/implant borne rehabilitation which can be used to create a stable occlusal fit with the new full-arch restoration of the upper jaw

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Unlikely to be able to comply with study procedures according to Investigators judgement
2. History of bone augmentation in the maxilla within 6 months prior to surgery
3. Uncontrolled pathologic processes in the oral cavity
4. Bruxism
5. Smoking >10 cigarettes per day
6. Present alcohol or drug abuse
7. History of radiation therapy in head and neck region
8. History of chemotherapy within 5 years prior to surgery
9. Condition that would compromise post-operative tissue healing or osseointegration
10. Bisphosphonates or any other medication that would compromise post-operative healing or osseointegration.
11. Known pregnancy at time of inclusion
12. Current or former participation in a clinical study that may interfere with the present study
13. Involvement in the planning and conduct of the study

Table of Contents

1 Introduction

1.1 Background

One of the primary goals of implant prosthodontics is to avoid removable prostheses. Especially edentulous patients are eager to replace their full upper dentures with implant borne fixed restorations [1]. However, a common result of edentulism in the upper jaw is severe bone atrophy of the alveolar ridge, causing a challenging situation for implant installation. Today, there are three main solutions to overcome the problem with limited bone volume to restore the upper jaw with implant borne dentures. Firstly, bone augmentation methods enable insertion of conventionally sized implants. Secondly, tilted implants use the residual posterior bone close to the sinus maxillaris. Thirdly, short implants can be used.

The third alternative with short implants offers a less invasive procedure than the two other alternatives, which is favourable both for the patient and the treating dentist [2]. For the patient, this means reduced pain, cost and chair time and for the dentist a less technically demanding procedure and a possibility to offer a prosthetic-driven implant placement. The usage of short dental implants ($l < 8.0$ mm) for replacement of missing teeth is currently increasing, both in the anterior and in the posterior regions [3]. The prevention of augmentative procedures [4] and thus the smaller, operational load has been shown to have a positive effect on elderly patients [5] and dentists with knowledge in implantology, but with limited experience, prefer cases where additional invasive steps are avoided.

Nevertheless, the effectiveness of short implants has been heavily debated during the last decades and the main criticism has concerned the limited surface area. The reason for this is that immediately after implant placement, there is merely a friction between the implant and bone, also called primary stability, keeping the implant in place. The primary stability increases with increasing length and diameter of the implant and thus, a short and simultaneously narrow implant cannot reach as high primary stability as a long or wide implant. In addition, the bone structure, in particular the relationship between the cortical and the cancellous portions, also affects the primary stability [6] and a large proportion of cancellous bone increases the risk of a reduced bone-to-implant contact and lack of primary stability at implant placement. In particular, this has been noticed in the maxilla where soft bone often is found [7]. Finally, implant thread design and surface roughness play a role, if a fit could be reached between processed bone cavity and implant to create a high primary stability. As a consequence, there are ways to increase primary stability also in challenging situations, e.g. in soft bone surgical protocols preparing bone cavities with smaller diameters than the implants can be used [8]. This, in combination with a screw-shaped implant with progressive threads, enables achievement of primary stability.

However, a low or complete lack of primary stability is not a problem for a secure osseointegration if no relative micro-motion can take place between bone and implant during the healing period. In other words, not the slightest load should be applied on an implant in case of missing primary stability. To assure avoidance of loading, the implant must heal submerged, and the implant platform should preferably be placed subcrestally.

Furthermore, a progressive bone training could be applied after submerged healing of short implants to improve the anchoring quality of the bone-to-implant interface to a point when a final restoration in functional occlusion can be installed [9]. After a successful osseointegration, the transferred load in the alveolar ridge leads to a reactive load-induced and -dependent remodeling of trabecular bone [10-12]. It causes an optimized anchoring of the implant in a three-dimensional network of trabeculae [13]. In summary, the load bearing capacity of implants differ between the healing period and after a fully load induced osseointegration. The type of contact within the implant-bone interface, non-bonded and bonded, undergoes a major change between the time of implant placement and the time of full load with a functional superstructure.

As a result of the continually adapting trabecular meshwork to ensure proper application of force in the alveolar bone [14], the above parameters of a purely frictional implant anchorage immediately after placement are not true anymore. In other words, implant diameter, length, surface and thread design are partially compensated by a mesh-like anchoring of the implant within the cancellous bone, in which a high load leads to an increased density of cancellous bone, and a small load to a thinning of the trabecular structure. The latter explains the proven long-term clinical success of narrow or short implants equal to conventional implants [15, 16].

Apart from the criticism regarding the smaller surface area of short implants, there have also been concerns about the high crown/implant ratio, which often is achieved when using short implants, and if this might increase the risk of marginal bone loss. A recent review shows that short implants with long

clinical crowns do not have more bone loss than implants with shorter crowns [17]. On the contrary, a reverse effect could be concluded: the longer the crown was in the vertical dimension, the less peri-implant bone loss was observed.

Despite the initial fears of using short implants, the advantages seem to outweigh the potential disadvantages. One of the greatest advantages is the possibility to place short implants in the upper jaw, thereby avoiding augmentation of the maxillary sinuses [18]. Short implants in the posterior regions and as anchors for single crowns show excellent clinical results [2, 19-21]. A systematic review and meta-analysis prove identical survival rates for short implants as of standard-length implants [22, 23]. However, one report exits about an increased risk of early failure for short implants when placed using template guided surgery [24].

The results from the above literature analysis prove the clinical success both of fixed full arch restorations concepts and of the use of shorter implants in the upper jaw. Therefore, the probability of obtaining good results when combining them both with a delayed loading is high. Especially the applied submerged healing in combination with a slight subcrestal placement of the implant platform [25] will protect the implant from overloading. The subcrestal placement reduces the crestal bone resorption [25, 26] and has an increased clinical impact for short implants too.

On the basis of a retrospective investigation of a patient data bank (based on prospective data set entry), the clinical long-term behaviour of 8 mm and 9.5 mm ANKYLOS implants in the posterior region was analysed. The data base collects since 1994 all patients at the dental clinic of the J. W. Goethe University supplied with implants, and is based on one annually assessment of all relevant parameters in dental implantology. For this evaluation solely ANKYLOS implants were included. 1055 implants with the length of 8.0 mm and 9.5 mm are recorded in the data base. Altogether, 552 implants were followed up in this study in a total of 379 patients.

The evaluation of the ANKYLOS implants with single tooth restorations shows a smaller crestal bone resorption for the 8 mm implants than for the 9.5 mm implants. Due to the positive clinical behaviour of short ANKYLOS implants, a good prognosis for ANKYLOS implants with a length of 6.6 mm can be derived.

The purpose of this study is to evaluate the ANKYLOS 6.6 mm implant when anchoring a fixed full arch bridge in the maxilla. Although the application of short implants has already been applied for several decades and a sufficient and safe anchorage quality can be achieved today, there are few clinical studies with six short implants in the upper jaw, which are splinted after the healing period by a fixed and screw-retained superstructure [27].

1.2 Study rationale

Short implants can reduce the need for augmentation, which significantly increases the number of potential implant patients, e.g. those who have financial limitations and/or fear of surgical augmentation procedures.

The objective of this prospective clinical study is to combine:

- the above mentioned advantage of a fixed full-arch bridge relating to an increased patient's satisfaction

with

- the advantages of short implants preventing or reducing the need of additional bone augmentation procedures to gain a sufficient bone amount for implant insertion

The main interest of this study is to assess the survival and the success rates of six short implants (6.6 mm) supporting maxillary fixed full-arch bridges after 5 years in function.

A further interest is focused on the question how many bone augmentation procedures can be prevented by using 6.6 mm long implants compared to 8 mm long implants.

The investigated therapy concept will not enable a split mouth design. A randomized clinical study with a control group with 8 mm implants is questionable due to ethical reasons. Participants randomly selected for the control group would suffer from more surgical interventions due to an increased probability of additional bone augmentation procedures. Therefore, a prospective, multi-center, single-arm study design was chosen, with the comparison between the 6.6 and 8 mm implant made virtually using the SIMPLANT® software system for 3D planning.

1.3 Risk/ benefit assessment

The results from the literature analysis prove that the bone anchorage of short implants for single tooth

restorations is sufficient, since no increased failure rates were evaluated. With no or minor resorption in crestal bone, the usage of short implants with 6 mm of length can be evidence-based recommended. Thus, the clinical relevance of the study results becomes accordingly high.

2 Study objectives

2.1 Primary objective

Primary Objective	Corresponding Primary Outcome Variable
Implant survival	Implant in situ during study

2.2 Secondary objectives

Secondary Objective(s)	Corresponding Secondary Outcome Variable(s)
Implant stability	Stability
Bone tissue response	Marginal Bone Level (MBL)
Soft tissue response	Plaque, Probing Pocket Depth (PPD) and Bleeding on Probing (BoP)
Patient reported outcomes	OHIP-14
Implant success	Implant in situ, no mobility, no pain, no exudates and <2 mm MBL alterations from Implant Placement to 5-year Follow-up visit
Prosthetic survival	Original restoration in place
Prosthetic success	No need of technical repair
Avoidance of augmentations	Number of sites (pre-defined) virtually suitable for 6.6 mm long v.s. 8.0 mm long implants (SIMPLANT®)

2.3 Safety objectives

Safety Objective(s)	Corresponding Safety Outcome Variable(s)
Safety events	Adverse Events (AE), Adverse Device Effects (ADE), Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE) and Device Deficiencies

3 Ethical and legal considerations

3.1 Ethics review

The responsibility for submissions and communication to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) is specified in the local agreements with each participating study site according to local requirements.

The final Clinical Investigation Plan (CIP), including the final version of the Informed Consent Form (ICF), must be approved by Regulatory Authority and/ or given a favorable opinion in writing by an IEC/IRB as appropriate before any subject can be enrolled into the study. Substantial Amendments must be submitted to the IEC/IRB and an approval must be obtained. Progress reports and

notifications of SAEs and SADEs will be provided to the IEC and/ or Regulatory Authorities according to local regulations and guidelines.

DENTSPLY Implants will provide the Principal Investigators with safety updates/reports according to local requirements.

3.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [28] and are consistent with ISO 14155 [29] and applicable regulatory requirements. The Sponsor and the Investigator are obliged to take over the responsibilities specified for both roles in the current ISO 14155.

3.3 Informed consent

The ICF must be approved by the responsible IEC/IRB prior to the study start.

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The Principal Investigator is responsible for ensuring that consent is given freely. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and sufficient time to consider the information provided. The subject's signed and dated informed consent must be obtained before any study specific procedure is performed.

The Principal Investigator must store the original, signed ICF in the Investigator Site File (ISF). A copy of the signed ICF must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by DENTSPLY Implants and by the responsible IEC/IRB.

3.4 Subject data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the data manager and DENTSPLY Implants will be identified by the study code and the subject id number. The ICF will also explain that for data verification purposes, authorized representatives of DENTSPLY Implants, a regulatory authority, an IEC/IRB may require direct access to parts of the hospital or practice records relevant to the study, including subject's medical history.

3.5 Insurance

Subjects participating in this clinical study are insured by DENTSPLY Implants, provided that the CIP and other written procedures are followed. For further details, see the Clinical Study Agreement (CSA).

4 Study design

4.1 Overall study design

This study is designed as a prospective, single-arm, multicentre study to document the outcome of the ANKYLOS A 6.6 implant when used in edentulous maxillas. For each subject, it will take approximately 6 months from study inclusion to installation of permanent restoration, followed by 5 years of follow-up. A total of 56 subjects will receive implants in the study and each center will have a

recruitment time of one year. Three to four centers will be included in the study. Subjects will be recruited among patients with edentulous upper jaws and restored/naturally dentured lower jaws.

4.1.1 Study duration

Anticipated First Patient In (FPI)	MAY/2015
Anticipated Last Patient In (LPI)	NOV/2016
Anticipated Last Patient Out (LPO)	MAY/2022
Anticipated Database Lock (DBL)	AUG/2022

4.2 Choice of outcome variables and study population

4.2.1 Choice of outcome variable

Implant survival will be evaluated by counting the number of implants still in place during the study. This has been chosen as primary outcome variable since clinical studies historically have reported lower survival rates for short implants (≤8 mm) [30-32]. However, two reviews evaluating more recent studies have shown that the survival rates for short implants are comparable with those obtained for longer implants placed under similar conditions, when using appropriate surgical technique and implants with a rough surface [33, 34]. Due to the short length of the 6.6 mm implant it is also probable that e.g. bone loss would result in implant loss rather quickly, turning implant survival to the most relevant variable.

4.2.2 Choice of study population

The edentulous maxilla has been chosen since the aim of the study is to evaluate if treatment with six 6.6 mm implants and fixed bridges could be a good alternative to angled, longer implants or bone grafting and longer implants. The edentulous maxilla presents one of the most challenging situations in implantology and if good results could be shown in this study, the chance is high that the 6.6 mm implant will perform well also in less challenging situations.

5 Study procedures

5.1 Study visits

The coded subject data will be documented in the electronic Case Report Form (eCRF) during the study. The table in Appendix B: Visit and procedure plan shows an overview of all study specific visits and procedures. The FDI digit system will be used, see Appendix C: Dental chart.

5.1.1 Visit 1, Screening and Inclusion

The subject will be informed orally and in writing about the study, and must have signed the ICF before any study specific procedures are performed (see section 3.3).

Treatment considerations for implant subjects should include an evaluation of:

- Oral health status (incl. periodontal status and restorative status)
- Medical status (anamnesis)
- Subject motivation
- Subject expectations of therapy outcome
- Risk factors

Clinical photos will be taken to document the subject's oral status before implant treatment.

The inclusion and exclusion criteria (section 5.3.3) will be considered (but can not be confirmed until after the CBCT and/or Implant Placement).

It must also be determined that the existing upper complete denture creates an adequate vertical dimension. Additionally, the upper complete denture has to be relined in case of a lack of fit to the soft tissue. The latter is an important step for the manufacturing of a well-fitting scan prosthesis.

5.1.2 Visit 2, Pre-surgical planning

A CBCT (Cone Beam Computed Tomography, a type of Digital Volume Tomography) will be performed as a reliable diagnostic tool for an exact planning and realization of implant insertion.

The CBCT will be used to determine that there is adequate height and width of bone to allow implant placement of six 6.6 mm implants and to ensure a sufficient oral and vestibular bone lamella width of at least 1.5 mm. The jaw should have an appropriate width of 5.5 mm in the implant area (implant diameter 3.5 mm + 2x1.0 mm).

Data from the CBCT will also be used for evaluating the number of avoided augmentations by using the 6.6 implants instead of the 8.0 mm implants in the SIMPLANT software system for 3D planning.

Clinical Work-Flow:

- Prepare a scan prosthesis by rebasing the existing prosthesis. Make 8 small, superficial cavities in the prosthesis' gingiva. Fill each cavity with a SIMPLANT Dual Scan Marker dipped in radiolucent resin. Let the resin cure. For further instructions, see SIMPLANT manual 'How to fabricate a scan prosthesis for the dual scan procedure'
- CBCT with scan prosthesis
- CBCT DICOM data transferred to SIMPLANT
- SIMPLANT file used by Investigator for bone related surgical planning. The Investigator will plan for placement of 6 short 6.6 mm implants in the canine, premolar and molar regions on both sides (one implant in each of the six regions). Caution should be taken to find the most optimal implant positions with regard to mesio-distal dimensions to assure placement in maximal bone amount available.
- Copy of SIMPLANT file sent to Evaluator for assessment of number of avoided augmentations when using 6.6 mm implants compared to 8.0 mm implants
- Oral health-related quality of life (OHIP-14) to be filled out by the subject

5.1.3 Visit 3, Implant Placement (IP)

Six short 6.6 mm implants will be placed in the implant positions defined at Visit 2 during the pre-surgical planning. Surgery should follow the guidelines for two-stage surgery described in the ANKYLOS 'Surgical Manual'.

After surgery, a CBCT will be taken to assure that no vulnerable anatomical structures (nerve, sinus, vessels etc.) have been hurt.

Clinical Work-Flow:

- Prepare 6 small crestal incisions, try to avoid big flaps
- Place 6 × A 6.6 implants (Ø 3.5 mm) slightly subcrestally, ensuring 0.5 mm subcrestal placement at the most apical peri-implant bone site
- If necessary, perform an internal sinus floor elevation. (If so, at least 5 mm of the implant should be placed in native bone. This could be done if detected during surgery that sinus floor elevation is necessary, instead of excluding the subject from the study.)
- Intra-operative check of subcrestally placed implant platform
- Mounting cover screws
- Clinical photos
- Submerged healing, 3 months
- CBCT
- Adaption of the base of the existing complete denture is not necessary

5.1.4 Visit 4, Post-op check (IP + 7-10 days)

Clinical Work-Flow:

- Post-op check

5.1.5 Visit 5, Abutment surgery + Impression (IP + 13 weeks, ± 10 days)

Clinical Work-Flow:

- Mucosal incisions
- Removal of cover screws
- Implant stability check. If implant is not stable, an individual decision should be made at the discretion of the Investigator. The recommendation is to let the implant sleep for 2-3 months, and if still not stable, remove and place a new 6.6 mm implant of wider diameter. If 5 implants remain, go for 5 in the bridge.
- Assembling of Balance Base Abutments C/ narrow. Abutment height should be chosen based on mucosa thickness. The recommendation is to place the abutment flange/shoulder epi gingival or even very slightly sub gingival.
- Assembling of Retention Copings for Balance Base Abutments C/ narrow
- Impression, using open-tray and an impression material of high accuracy, becoming stiff after curing
- Disassembling of the Retention Copings
- Closing the screw holes of Balance Base Abutments with wax
- Clinical photos
- Adapting the base of the existing full denture to avoid loading of any of the six implants

Dental-Lab Work-Flow:

- Production of master cast
- Production of template for jaw relation recording

5.1.6 Visit 6, Bite registration (IP + 14 weeks, ± 5 days)

Clinical Work-Flow:

- Horizontal and vertical jaw relation record by using the dental lab produced template
- Face-bow transfer

Dental-Lab Work-Flow:

- Mounting study casts into articulator (using face bow)
- Production of a wax based esthetic teeth arrangement
- Ordering ATLANTIS ISUS framework
- Production of a try-in of esthetic teeth arrangement based on ATLANTIS ISUS framework

5.1.7 Visit 7, Try in of ATLANTIS ISUS framework + esthetic teeth arrangement (IP + 16 weeks, ± 2 weeks)

Clinical Work-Flow:

- Try in
- New jaw relation record

Dental-Lab Work-Flow:

- Finishing the final full-arch bridge

5.1.8 Visit 8, Insertion of final Prosthetic Restoration, PR (IP + 17 weeks, ± 2 weeks)

Clinical Work-Flow:

- Insertion of the final full-arch bridge (for specification of material, see section 8)
- Adaptation of occlusion (canine guided)
- Soft tissue response (Plaque, PPD, BoP)
- Intra-oral x-rays
- Clinical photos
- OHIP-14 to be filled out by the subject

5.1.9 Visit 9, 6-month Follow-up (PR + 6 months, ± 2 weeks)

- Clinical photos
- Implant survival
- Soft tissue response (Plaque, PPD, BoP)
- Prosthetic survival
- Prosthetic success

5.1.10 Visit 10, 12-month Follow-up (PR + 12 months, ± 1 month)

- Intra-oral x-rays
- Clinical photos
- Implant survival
- Soft tissue response (Plaque, PPD, BoP)
- Prosthetic survival
- Prosthetic success
- OHIP-14

5.1.11 Visit 11, 24-month Follow-up (PR + 24 months, ± 1 month)

- Clinical photos
- Implant survival
- Soft tissue response (Plaque, PPD, BoP)
- Prosthetic survival
- Prosthetic success

5.1.12 Visit 12, 36-month Follow-up (PR + 36 months, ± 1 month)

- Intra-oral x-rays
- Clinical photos
- Implant survival
- Soft tissue response (Plaque, PPD, BoP)
- Prosthetic survival
- Prosthetic success
- OHIP-14

5.1.13 Visit 13, 48-month Follow-up (PR + 48 months, ± 1 month)

- Clinical photos
- Implant survival
- Soft tissue response (Plaque, PPD, BoP)
- Prosthetic survival
- Prosthetic success

5.1.14 Visit 14, 60-month Follow-up and Study Completion (PR + 60 months, ± 1 month)

- Intra-oral x-rays
- Clinical photos
- Implant survival
- Implant success
- Soft tissue response (Plaque, PPD, BoP)
- Prosthetic survival
- Prosthetic success
- OHIP-14

5.2 Compliance

Subjects will be asked to return to all visits and to follow the Investigator's instructions regarding the treatment at any time (post-surgery activities etc.). Non-compliance is defined as subjects obviously disregarding the Investigator's instructions. Subjects judged to be non-compliant may continue in the study for safety reasons, but the reimbursement of the treatment will be reduced as described in the CSA.

5.3 Study population

5.3.1 Selection records

The Investigator(s) must keep a Screening Log of subjects who were considered for inclusion. Subjects listed on that log are either included or failed to fulfill selection criteria, so called 'Screening failures'.

This information is necessary to establish that the subject population was selected without bias.

5.3.2 Identification records

The Investigator(s) must also keep and maintain a Subject Identification Log with e. g. full name, date of birth, subject id etc. of all subjects who have been enrolled and treated within the scope of the study. This information is necessary to be able to identify the participating subjects.

The Subject Identification Log remains on site and will neither be collected nor copied by DENTSPLY Implants.

5.3.3 Subject-selection criteria

5.3.3.1 Inclusion criteria

For inclusion in the study subjects must meet all of the following criteria:

1. Aged 18-80 years at inclusion
2. Signed informed consent
3. In need of full-arch restoration of the maxilla

The following should be considered at inclusion but need to be fulfilled at Implant Placement (Visit 3):

4. Maxilla: totally edentulous, fulfilling all of the following criteria:
    a) History of edentulism: ≥ 6 months and
    b) Minimum bone height: ≥ 7 mm and
    c) Minimum bone width: ≥ 5.5 mm
5. Mandible: antagonistic natural dentition or tooth/implant borne rehabilitation which can be used to create a stable occlusal fit with the new full-arch restoration of the upper jaw

5.3.3.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Unlikely to be able to comply with study procedures according to Investigators judgement
2. History of bone augmentation in the maxilla within 6 months prior to surgery
3. Uncontrolled pathologic processes in the oral cavity
4. Bruxism
5. Smoking >10 cigarettes per day
6. Present alcohol or drug abuse
7. History of radiation therapy in head and neck region
8. History of chemotherapy within 5 years prior to surgery
9. Condition that would compromise post-operative tissue healing or osseointegration
10. Bisphosphonates or any other medication that would compromise post-operative healing or osseointegration.
11. Known pregnancy at time of inclusion
12. Current or former participation in a clinical study that may interfere with the present study
13. Involvement in the planning and conduct of the study

5.4 Restrictions

Restrictions regarding hygiene measures, use of subject's existing prosthesis and food intake will be given in accordance with the clinic's local routines.

5.5 Discontinuation of subjects from study

5.5.1 Criteria for discontinuation

Subjects may be discontinued from the study at any time. Specific reasons for discontinuing a subject include:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the Investigator or the sponsor
- Severe non-compliance to the CIP as judged by the Investigator and/or the sponsor
- Subject lost to follow-up (as defined by the inability to reach the subject after 3 attempts to contact him/her, e.g. by phone, email, or letter; all should be documented in the subject's medical records)
- Loss of all study implants

5.5.2 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any safety issues. If possible, they should be seen and assessed by an Investigator. The Termination section in the eCRF should be completed. AEs should be followed up.

After discontinuation, appropriate further treatment will be initiated according to the Investigator's judgment and according to local medical practice.

5.5.3 Procedure for handling enrolled subjects that fail to fulfill inclusion/ exclusion criteria

If a subject has been enrolled, but no study-related surgical procedures were performed (withdrawal of consent, not meeting all pre-surgical criteria etc.) the Investigator must document this in the subject's medical records. In case of the subject's unavailability the Investigator will document this as well. Termination section in the eCRF should be completed. No follow-up is necessary.

If a subject has been enrolled and study-related surgery started, but for any reason no Investigational Product could be inserted the Investigator must document this in the subject's medical records. Termination section in the eCRF should be completed. No follow-up is necessary.

If a subject has been enrolled and study-related surgery has been completed, although the inclusion/ exclusion criteria are violated, it will be decided on a case-by-case basis by DENTSPLY Implants if the subject will continue in the study. If so, the subject will not be part of the Intention-to-Treat (ITT) analysis and the reimbursement of the treatment will be reduced as described in the CSA.

If a subject lose a study implant and a new implant is inserted, the new implant should not be registered in the eCRF. If a subject loses all study implants, the subject will discontinue the study.

6 Study methodology

6.1 Prior and concomitant treatment(s)

An antibiotic prophylaxis is not obligatory due to the minimal surgical intervention.

For prohibited medication, see Exclusion Criteria section 5.3.3.2.

6.2 Demographics and other baseline characteristics

- Date of birth
- Sex
- Relevant medical and surgical history
- Medication at entry and during the study
- Nicotine use
- Oral examination including dentition of opposing jaw
- Edentulous period

- Reason for edentulism
- Bone quantity and quality (Visit 3)

6.3 Assessments of outcome variables

6.3.1 Primary outcome variable

Implant survival rate

6.3.1.1 Assessment of primary outcome variable

Implant survival will be evaluated clinically and radiographically by counting the number of implants remaining *in situ*. Any implant that has been removed or lost after implant placement (Visit 3) will be considered a failure, whatever the reason for removal/loss.

Implant survival rate will be analyzed on an implant level (i.e. percent of survived implants) as well as subject level (i.e. percentage of subjects with no lost implants).

6.3.2 Secondary outcome variables

6.3.2.1 Secondary outcome variable(s)

- Implant stability
- Marginal Bone Level alterations
- Soft tissue response (Plaque, PPD, BoP)
- OHIP-14
- Implant success
- Prosthetic survival
- Prosthetic success
- Number of avoided augmentations

6.3.2.2 Assessment of secondary outcome variable(s)

- *Implant stability*

  Implant stability will be evaluated clinically/manually at implant placement (primary stability) and at abutment surgery and recorded as yes/no.

- *Marginal Bone Level alterations*

  Bone level response will be evaluated from intra-oral radiographs. To ensure good quality and reproducibility between the examinations, the below instructions must be followed:
  - Standardized long-cone parallel technique should be used
  - Film holders should be used
  - The radiographic beam should be perpendicular to the implant and film
  - The threaded profile of the marginal portion of the implant, both mesially and distally, must be clearly visible.
  - If pathology around the implant is suspected, supplementary periapical x-rays should be taken.
  - Double film and/or digital radiographs may be used and a hard copy or electronic copy of the image will always be retained on site for future reference.
  - ***Radiographs must be marked with subject id, visit no, date and implant positions*** before uploading/sending them to DENTSPLY Implants. No subject names or birth dates should be visible on the radiographs.

  The radiographs will be sent for central evaluation to a radiologist who is independent from the investigational group and DENTSPLY Implants. The radiologist will measure and record the

distance from a reference point on the implant to the most coronal bone-to-implant contact on the mesial and distal aspect of the implant. Peri-implant radiolucency will be registered as present or absent. The reference point is defined as the implant shoulder.

The mean marginal bone levels will be calculated for each implant as well as for each subject and used for further analysis. The alteration in the marginal bone level from baseline (Visit 8, Prosthetic Restoration) to each time point will be calculated.

- *Soft tissue response (Plaque, PPD and BoP)*

  Plaque will be recorded as presence or absence of plaque by visual inspection on four surfaces at each implant site (mesially, distally, buccally and lingually). PPD and BoP will be evaluated at the same four surfaces around the implant, by using a periodontal probe. PPD will be measured as the distance from the mucosal margin to the bottom of the probeable pocket in mm. BoP will be recorded as presence or absence of bleeding when probing to the bottom of the pocket.

- *OHIP-14*

  Patient satisfaction will be evaluated using the Oral Health Impact Profile 14 (OHIP-14). The questionnaire will be filled in by the subjects before and after treatment with implants.

  OHIP-14 includes seven domains and is therefore able to cover a wide range of possible oral health problems that may have an impact on quality of life. The domains are: functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. OHIP attempts to measure both the frequency and severity of oral problems on functional and psychosocial well-being. An example of an OHIP statement is "Have you had to interrupt meals because of problems with your teeth, mouth or dentures". Responses are based on a Likert scale (i.e., 0 = never, 1 = hardly ever, 2 = occasionally, 3 = fairly often, 4 = very often).

- *Implant success*

  Implant success will be evaluated as defined by the ICOI Pisa Consensus Conference 2008 [35]. An implant will be considered successful if all of the following criteria are fulfilled:
  - Implant still in place
  - No mobility
  - No pain or tenderness upon function
  - <2 mm marginal bone loss from initial surgery to 5-year follow-up visit
  - No history of exudates

- *Prosthetic survival*

  A prosthetic restoration will be considered a *survivor* if the original restoration is still in place at the follow-up visit, regardless of its condition.

- *Prosthetic success*

  A prosthetic restoration will be considered as successful if it has remained unchanged and there has been no need of technical repair during the observation period.

  The occurrence of any technical repair of the prosthesis or any biological complications related to the prosthesis will be registered and reported as ADEs (section 6.4.1.2).

- *Number of avoided augmentations*

  The proportion of augmentations avoided by using six 6.6 mm implants instead of six 8.0 mm implants will be virtually evaluated by using the SIMPLANT file generated from the CBCT at Visit 2. First, six regions of interest will be defined in SIMPLANT by indicating the mesial and distal borders of the canine, premolar and molar regions on both left and right side. An evaluator, independent from the investigational group and DENTSPLY Implants, will then make a surgical planning with six 6.6 mm implants placed at the pre-defined canine, premolar and molar regions and count the number of sites that would need augmentation. The evaluator will then repeat this

procedure but now use six 8.0 mm implants for the planning. If necessary, the evaluator will be allowed to exceed the region borders slightly when doing the surgical planning, in order to achieve maximal bone amount (to reflect the real situation).
The difference in number of needed augmentations for the 8.0 mm implants and the 6.6 mm implants divided by the number of needed augmentations for the 8.0 mm implants will represent the proportion of augmentations avoided by using the 6.6 mm implant.

6.4 Safety measures

6.4.1 Types of safety events

The below definitions are based on ISO 14155.

6.4.1.1 Adverse Event (AE)

Any untoward medical or dental occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the Investigational Product or the procedures involved.

For users or other persons, this definition is restricted to events related to the Investigational Product.

DENTSPLY Implants clarification: Not only the Investigational Product, but also other medical devices used in the study, for example abutments and prosthetic parts should be included in the AE reporting.

A ‘subject’ is a patient who is treated within the frame of a clinical study.

A ‘user’ is a person handling the medical device, for example the dentist, nurse or assistant.

‘Other persons’ are someone else present in the room during the treatment, for example a friend of the patient.

6.4.1.2 Adverse Device Effect (ADE)

AE related to the use of an Investigational Product.

This includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. This includes any events resulting from use error or from intentional misuse of the device.

DENTSPLY Implants clarification: Not only the Investigational Product, but also other medical devices used in a study, for example abutments and prosthetic parts should be included in the ADE reporting.

6.4.1.3 Serious Adverse Event (SAE)

An SAE is an AE that:

- Led to death,
- Led to a serious deterioration in the health of a subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization (Hospital admissions and/or surgical operations that were planned before or during the study for a pre-existing condition, without serious deterioration in health, is NOT considered an SAE), 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.

6.4.1.4 Serious Adverse Device Effect (SADE)

An SADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

6.4.1.5 Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labeling.

NB! Pay special attention to device deficiencies that might have led to an SADE if:

a) suitable action had not been taken or
b) intervention had not been made or
c) circumstances had been less fortunate.

DENTSPLY Implants clarification: A device deficiency is an event associated with the product itself, not with the subject. The loss of an implant is not defined as a device deficiency; it is defined as an ADE.

6.4.2 AE and ADE recording and reporting

In clinical studies, an AE can include a health/oral problem occurring at any time, including run-in or follow-up periods, even if the subject has not been exposed to the medical device.

Subjects will be observed and asked about 'any health or oral health problems since last visit' during the study.

All health/oral problems, reported by the subject, found in medical records or found at the clinic visits, must be recorded in the eCRF as an AE. Information that will be collected includes:

- Event description
- Start date
- Stop date or event continuing
- Serious yes/no
- Device/procedure related yes/no
- Action taken due to the event
- Clinical outcome of event

If an AE is assessed to be device/procedure related it is defined as an ADE. For ADEs the Investigator must:

- record ADE details in the eCRF as soon as he/she becomes aware of it, an e-mail will automatically be sent to DENTSPLY Implants

If an AE/ADE results in a subject's discontinuation in the study, this should be recorded on the Termination page in the eCRF. Not only the Investigational Product, but also other medical devices used in a study, for example abutments and prosthetic parts should be included in the ADE reporting.

Examples of AEs are e.g. cold, headache and abutment loss at non-study positions.

Examples of ADEs are e.g. implant loss, implant fracture, abutment loss, abutment fracture, abutment screw fracture, abutment loose, bridge screw loose/fractured at study positions.

6.4.3 SAE and SADE recording and reporting

SAEs and SADEs have to be reported to DENTSPLY Implants as soon as the Investigator becomes aware of it.

For SAEs/SADEs the Investigator must:

- Record SAE/SADE details in the eCRF immediately, but no later than the end of the next business day (counting from when the Investigator becomes aware of the SAE/SADE), an e-mail will automatically be sent to DENTSPLY Implants
- Follow up the initial SAE/SADE information as soon as new information is available.
- Inform the responsible IEC/IRB of SAEs/SADEs, as per local requirements. This may involve both those SAEs/SADEs occurring at the study site as well as at other participating study sites (this information will be provided to the Investigator by DENTSPLY Implants, if required).
- Inform the responsible Regulatory Authority of SAEs/SADEs, as per local requirements. This may involve both those SAEs/SADEs occurring at the study site as well as at other participating study sites (this information will be provided to the Investigator by DENTSPLY Implants, if required).
- Provide DENTSPLY Implants with all SAE/SADE related documentation and correspondence to the IEC/IRB and Regulatory Authority

In addition, further attempts to speak directly with DENTSPLY Implants should be made by dialing the following phone no: +46 31 376 35 00 and ask for responsible STL.

A copy of the SAE/SADE Report and associated documents must be filed in the ISF by the Investigator.

Examples of SAEs are e.g. broken leg requiring hospital admission and heart attack.

6.4.4 Device Deficiency Reporting

The Investigator is responsible for recording the following in the eCRF for all device deficiencies:

- Device deficiency details (e. g. date and description of occurrence)
- Whether the device deficiency led or could have led to a SADE

Pay special attention to device deficiencies that might have led to a SADE if:

a) suitable action had not been taken or

b) intervention had not been made or

c) circumstances had been less fortunate

For device deficiencies that fulfil the SADE definition the Investigator must complete and provide DENTSPLY Implants with detailed information and perform the steps described for SAE/SADE reporting.

An example of a device deficiency is when the packaging around the implant is damaged.

6.4.5 Safety event follow-up

Medical follow-up of any type of safety event will continue until the abnormality resolves, or an adequate medical explanation is apparent.

Documentation of all follow-up information regarding the AEs must be provided in the eCRF and, in accordance to the reporting requirements described above.

If the subject is withdrawn from study treatment due to an AE, the AE and the reason for withdrawal from the study is to be documented clearly in the eCRF.

7 General study management

Study Start is not allowed before all of the necessary approval documents (IEC/IRB approval, signed CIP, signed CSA, regulatory approval if applicable) are available and the study site has been initiated by DENTSPLY Implants.

7.1 Changes to the Clinical Investigation Plan (CIP)

Study procedures will not be changed without the mutual agreement of the coordinating Investigator and DENTSPLY Implants. If it is necessary for the CIP to be amended, the amendment and/or a new version of the CIP (Substantial Amendment) must be notified to or approved by each IEC/IRB, and if applicable, also the local Regulatory Authority, before implementation. Local requirements must be followed. If a CIP amendment requires a change to a particular study site's ICF, then DENTSPLY Implants and the study site's IEC/IRB must be notified. Approval of the revised ICF by DENTSPLY Implants and by the IEC/IRB is required before the revised form is used. DENTSPLY Implants will distribute amendments and new versions of the CIP to each Principal Investigator(s), who in turn is responsible for the distribution of these documents to his or her IEC/IRB, and to the staff at his or her study site. The distribution of these documents to the Regulatory Authority will be handled according to local practice.

In general, a Non-substantial Amendment does not require a notification to or approval by IEC/IRB.

7.2 Monitoring

Before the first subject enters the study, a representative of DENTSPLY Implants will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved in the study) their responsibilities with regard to CIP adherence, and the responsibilities of DENTSPLY Implants or its representatives.

During the course of the study, a study monitor from DENTSPLY Implants or representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the CIP, that data are being accurately recorded in the eCRFs, and that Investigational Product accountability checks are being performed
- Perform source data verification (SDV, a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject.

The study monitor or another DENTSPLY Implants representative will be available between visits if the Investigator(s) or other staff at the study site needs information and advice.

7.3 Audits and inspections

Authorized representatives of DENTSPLY Implants, a Regulatory Authority, an IEC/IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of a DENTSPLY Implants audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the CIP, ISO 14155 and any applicable regulatory requirements. The Investigator should contact DENTSPLY Implants immediately if contacted by a regulatory agency about an inspection at his or her site.

7.4 Training of study site staff

The Principal Investigator must maintain a record of all individuals involved in the study (medical, nursing and other staff), i.e. a Responsibility and Signature Log. He or she shall ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved. DENTSPLY Implants will support the training.

Before the first subject is entered into the study, the study staff will be trained to use the EDC system (eCFR) by DENTSPLY Implants personnel or delegates.

7.5 Deviations from the Clinical Investigational Plan

The Investigator is not allowed to deviate from the CIP except in emergency situations, with purpose to protect a subject's rights, safety and wellbeing.

In such cases, the Investigator may proceed without prior approval of DENTSPLY Implants and the EC. Furthermore, such deviations shall be documented and reported as soon as possible to DENTSPLY Implants and the IEC.

Should the Investigator break any obligations under the CIP or CSA (including a failure without just cause to meet a timeline) and fail to remedy such a breach where it is capable of cure, DENTSPLY Implants retains the right to disqualify the study site from further study participation.

All CIP deviations must be directly reported to the Study Team Leader, by either the Investigator or Monitor.

7.6 Study agreements

The Principal Investigator at each study site should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CIP and the CSA, the terms of CIP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between DENTSPLY Implants and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

7.7 Early termination of the study

The end of the study is defined as ‘the last visit of the last subject undergoing the study’.

The study may be terminated at individual study sites if the study procedures are not being performed according to regulations (Declaration of Helsinki, ISO 14155 and applicable regulatory requirements) or if recruitment is slow. DENTSPLY Implants may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with the Investigational Product.

7.8 Publication policy

The results from the SIMPLANT evaluation (no. of avoided augmentations) as well as the 1-, 3- and 5-year data are planned to be compiled into articles and submitted to peer-reviewed journals. The data will be provided by DENSTPLY Implants and the writing process will be coordinated by the International Co-ordinating Investigator.

8 Investigational Products

Product Name	ANKYLOS® C/X Implant A 6.6
Diameter	3.5 mm
Lengths	6.6 mm
Characteristics	Dental endosseous implant

Packaging	Sterile, double package
Other products	
Cover screws	ANKYLOS® C/X Cover Screw
Abutments	ANKYLOS® Balance Base Abutment C/ narrow – available in four heights, i.e. 0.75, 1.5, 3.0 and 4.5 mm. Both the straight (A0) and the 15° angled (A15) abutments are allowed in the study. NB! The 30° angled versions (A30) are not allowed in the study.
Suprastructure	Occlusally screw-retained ATLANTIS™ ISUS bridges (titanium)
Veneering	Subjects will, in consultation with the Investigator, be able to choose one out of four alternatives: • Resin • Composite • Composite and Ceramic • Ceramic

8.1 Indications for use

ANKYLOS C/X 6.6 mm implants are intended for replacing missing teeth and for supporting single tooth restorations, bridges and prostheses (overdentures) to restore chewing function of the patient.

8.2 Labeling

The packing and labeling of the Investigational Product will be performed by DENTSPLY Implants in accordance with ISO 14155. The labels will be available in English language and in accordance with local regulations.

8.3 Storage and accountability records

All Investigational Products must be kept in a dry and secure (locked) area. Investigational Products will be used only for this study and only in accordance with the CIP.

The Principal Investigator is responsible for maintaining accurate records (Device Accountability Form) of the dispensing of Investigational Products. Any Investigational Products accidentally or deliberately destroyed must be accounted for and discrepancies between amounts dispensed and returned should be explained. All unused products must be returned to DENTSPLY Implants when treatment of the last subject has been completed.

9 Data collection and data management

9.1 Case Report Form recording and processing

Data will be entered into electronic Case Report Forms (eCRFs) using Viedoc™, a web based Electronic Data Capture (EDC) system used by DENTSPLY Implants, at the study site. Trained and authorized study site personnel will be responsible for entering data into Viedoc™. Data entered into Viedoc™ will be immediately saved to a central database, hosted by a 3rd party, PCG Solutions.

When data has been entered, reviewed, edited and source data has been verified, the data will be locked to prevent further editing and, if not already done, the Principal Investigator will be prompted to sign the eCRF electronically. A contemporaneous copy of the CRF must be available for the study site.

Data queries will be raised for inconsistent, impossible or missing data. The study site personnel are required to resolve any such queries. All entries to the study database will be available in an audit trail.

Results from central evaluations of CBCT-scans/SIMPLANT files and X-rays will be entered directly into Viedoc™ by DENTSPLY Implants personnel or the evaluators.

When data verification and validation is complete and data is deemed clean, clean file will be declared. Any treatment revealing data may thereafter be added and the database will be locked.

9.2 Storage of data

Readable copies of the eCRF data, stored on a CD-ROM or a DVD will be archived in the ISF at the study site after Clean File. The ISF copy will be created either by 3rd party, PCG Solutions or by trained study site personnel. DENTSPLY Implants will not at any time point be in control of the ISF data archive, unless the copy is sealed by 3rd party and then only for the purpose of delivering it to the study site.

DENTSPLY Implants will assume responsibility for the long-term storage of all data in compliance with the applicable local laws and ISO 14155 [29].

Study data will be securely stored at DENTSPLY Implants, with restricted access. Data will be retained at DENTSPLY Implants for 25 years after study closure.

10 Statistical methods and data analysis

10.1 Statistical evaluation – general aspects

When using the terminology descriptive statistics it is meant that the number of subjects (N), mean, median, standard deviation (SD), minimum (min) and maximum (max) values will be presented for continuous data and frequencies and percentages for categorical data. If nothing else is stated, descriptive statistics will be given for each variable in the study.

When calculating p-values a non-parametric statistical approach will be applied because of the nature of the data. Confidence interval will be calculated using distribution assumptions.

No sub-groups are defined but it cannot be ruled out that such are defined during the conduct of the study or in the analysis of the study data. The statistical analysis will then follow the intentions presented in this section and the possibility of multiplicity will be considered.

10.1.1 Demographics and other baseline characteristics

Demographics and other baseline characteristics will be presented by means of descriptive statistics.

10.1.2 Covariates and prognostic variables

No covariates are judged to influence the outcome of the primary or any of the secondary variables.

10.1.3 Handling of dropouts and missing data

Subjects dropping out from the study during the recruitment period will be replaced. Subjects dropping out after completion of the recruitment period will not be replaced but compensated for in the sample size estimation, see section 10.4.

10.1.4 Multi-center

This study is a multi-center study. However, there is no a priori reason to suspect that there will be any qualitative differences between the study sites regarding any of the efficacy variables nor regarding

the safety variables. Therefore the primary statistical analysis will not include study sites in the model but the result of the primary variable will as well be presented by study site.

10.2 Description of analysis sets

The study will be analyzed using a Safety (S) and an Intention-to-Treat (ITT) population approach. The S analysis set will consist of all included subjects who have been treated with implants. ITT analysis set will consist of all subjects fulfilling the inclusion criteria, none of the exclusion criteria and have had their implants installed as planned. Treatment efficacy related conclusions will be based on the results from the ITT analysis.

All subject data will be included in subject data listings.

10.3 Method of statistical analysis in relation to objectives

If nothing else is stated, descriptive statistics will be given for each variable in the study and p-values may be complemented by confidence intervals as appropriate.

All p-values presented will be two-sided. A p-value less than 5% will be called “statistically significant” but all conclusions will be based on the primary objective and hence multiplicity is accounted for even though careful interpretations are necessary as multiple tests are performed. No formal adjustment for multiplicity will be applied and nominal p-values will be presented. All confidence interval will be two-sided and 95%.

When calculating p-values a non-parametric statistical approach will be applied because of the nature of the data. Confidence interval will be calculated using distribution assumptions.

The primary objective will be analysed using the exact Binomial test and a parametric confidence interval for the true proportion of implants surviving will be presented

The safety profile will be analysed using descriptive statistics only.

The planned statistical methods for the efficacy evaluation is presented by objective below:

Primary Objective	**Corresponding Primary Outcome Variable**	**Statistical Method**
Implant survival	Implant in situ during study	The exact Binomial test and a parametric confidence interval for the true proportion of implants surviving will be presented

Secondary Objective(s)	**Corresponding Secondary Outcome Variable(s)**	**Statistical Method**
Implant stability	Stability	A parametric confidence interval for the true proportion of implants with stability = “yes” will be presented
Bone tissue response	Marginal Bone Level (MBL)	The change over time will be tested using the Wilcoxon signed rank test and a parametric confidence interval presented.
Soft tissue response	Plaque, Probing Pocket Depth (PPD) and Bleeding on Probing (BoP)	The change over time will be tested using the Wilcoxon signed rank test and a parametric confidence interval presented.
Patient reported outcomes	OHIP-14	The change over time will be tested using the Wilcoxon signed rank test and a parametric confidence interval presented.

Secondary Objective(s)	Corresponding Secondary Outcome Variable(s)	Statistical Method
Implant success	Implant in situ, no mobility, no pain, no exudates and <2 mm MBL alterations from Implant Placement to 5-year Follow-up visit	A parametric confidence interval for the true proportion of implants with success = "yes" will be presented
Prosthetic survival	Original restoration in place	A parametric confidence interval for the true proportion of restorations in place = "yes" will be presented
Prosthetic success	No need of technical repair	A parametric confidence interval for the true proportion of restorations with need of technical repair = "no" will be presented
Avoidance of augmentations	Proportion of augmentations avoided by using six 6.6 mm implants instead of six 8.0 mm implants (SIMPLANT®)	A parametric confidence interval for the true proportion of augmentations when using six 8.0 mm implants but not when using six 6.6 mm implants.

10.4 Determination of sample size

In this study each subject will get 6 implants. However, in the statistical analysis the implants will be assumed to be independent and therefore used as the statistical unit.

Clinical studies with follow-up periods of 1-17 years report survival rates ranging between 93 and 100% for ANKYLOS implants ≥ 8 mm [36-39]. A recently completed study on implant treatment of the edentulous maxilla with the ASTRA TECH Implant system (length 8-17 mm) reported a survival rate of 93% after 5 years (data not yet published). There is no indication that the survival rate for the ANKYLOS 6.6. mm implant would differ from the longer ANKYLOS implants and due to the similarity with the ASTRA TECH study mentioned above, the true five-year survival rate for the 6.6 mm ANKYLOS implant is assumed to be 93%-95%.

The aim of the study is to show that the implant survival rate is not less than π_1. This means that the null-hypothesis H_0: $\pi < \pi_1$ will be tested and if rejected (i.e. the one-sided p-value is less than 0.0250) the alternative hypothesis, i.e. H_1: $\pi \geq \pi_1$, will be accepted. The test to be used is the exact Binomial test.

As the assumed implant failure rates are close to 0 it cannot be assumed normal approximation is valid and hence exact methods for sample size determination is applied by means of StatXact (version 10.1).

In Table 1, the total number of implants needed in order to reach 80% and 90% power to reject the null-hypothesis is given when assuming true implant survival rates between 93% and 95%.

Table 1 Number of needed implants in order to test the null hypothesis that the survival rate is at least π_1 by power 80% and 90% and by true survival rate between 93% and 95%. The number of subjects is given by dividing the number of implants by 6. (by StatXact, version 10.1)

Power	π_1	True survival rate (π)		
		0.93	0.94	0.95
80%	0.85	135	102	75
	0.88	292	191	139
	0.90	719	398	242
90%	0.85	176	135	102
	0.88	380	252	180
	0.90	942	503	304

As seen in Table 1, a total of 304 implants will be needed in order to reach 90% power to reject the null-hypothesis that the survival rate is less than 90% if the true implant survival rate is 95%. Since each subject will receive 6 implants, this means that a total of 304/6=51 fully evaluable subjects will be required.

In this subject population we expect a 10% drop-out rate from the study over a 5-year period. In order to ensure 51 evaluable subjects, 56 subjects will receive implants in the study.

10.5 Statistical analysis during the course of the study

Partial clean file is planned to be declared when all subjects have completed:

- Visit 2 (CBCT) – data will be used for publication describing no. of avoided augmentations by using 6.6 mm implants instead of 8 mm implants (virtually evaluated in SIMPLANT file from CBCT taken before implant placement).
- Visit 10 (1-year follow-up) – data will be used for 1-year follow-up publication.
- Visit 12 (3-year follow-up) – data will be used for 3-year follow-up publication.

Data base lock will take place and total clean file will be declared when all subjects have completed:

- Visit 14 (5-year follow-up) – data will be used for 5-year follow-up publication.

List of abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
BoP	Bleeding on Probing
CBCT	Cone Beam Computed Tomography
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSA	Clinical Study Agreement
DBL	Database Lock
DD	Device Deficiency
DI	DENTSPLY Implants
EDC	Electronic Data Capture
FDI	Fédération Dentaire Internationale
FPI	First Patient In
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IP	Implant Placement
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
LPI	Last Patient In
LPO	Last Patient Out
MBL	Marginal Bone Level
OHIP	Oral Health Impact Profile
PPD	Probing Pocket Depth
PR	Prosthetic Restoration
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification

List of references

1. Pommer, B., et al., *Patients' preferences towards minimally invasive treatment alternatives for implant rehabilitation of edentulous jaws.* Eur J Oral Implantol, 2014. **7 Suppl 2**: p. S91-109.
2. Thoma, D.S., et al., *Randomized controlled multicentre study comparing short dental implants (6 mm) versus longer dental implants (11-15 mm) in combination with sinus floor elevation procedures. Part 1: demographics and patient-reported outcomes at 1 year of loading.* J Clin Periodontol, 2015. **42**(1): p. 72-80.
3. Queiroz, T.P., et al., *Clinical study on survival rate of short implants placed in the posterior mandibular region: resonance frequency analysis.* Clin Oral Implants Res, 2014.
4. Felice, P., et al., *Treatment of the atrophic edentulous maxilla: short implants versus bone augmentation for placing longer implants. Five-month post-loading results of a pilot randomised controlled trial.* Eur J Oral Implantol, 2011. **4**(3): p. 191-202.
5. Muller, F., et al., *Implant-supported mandibular overdentures in very old adults: a randomized controlled trial.* J Dent Res, 2013. **92**(12 Suppl): p. 154s-60s.
6. Akca, K., et al., *Biomechanical aspects of initial intraosseous stability and implant design: a quantitative micro-morphometric analysis.* Clin Oral Implants Res, 2006. **17**(4): p. 465-72.
7. Monje, A., et al., *Influence of Atrophic Posterior Maxilla Ridge Height on Bone Density and Microarchitecture.* Clin Implant Dent Relat Res, 2013.
8. Anitua, E., et al., *Efficacy of biologically guided implant site preparation to obtain adequate primary implant stability.* Ann Anat, 2014.
9. Ghoveizi, R., et al., *A radiographic comparison of progressive and conventional loading on crestal bone loss and density in single dental implants: a randomized controlled trial study.* J Dent (Tehran), 2013. **10**(2): p. 155-63.
10. Berglundh, T., et al., *De novo alveolar bone formation adjacent to endosseous implants.* Clin Oral Implants Res, 2003. **14**(3): p. 251-62.
11. Huiskes, R., et al., *Effects of mechanical forces on maintenance and adaptation of form in trabecular bone.* Nature, 2000. **405**(6787): p. 704-6.
12. Ruimerman, R., et al., *A theoretical framework for strain-related trabecular bone maintenance and adaptation.* J Biomech, 2005. **38**(4): p. 931-41.
13. Wirth, A.J., R. Muller, and G.H. van Lenthe, *The discrete nature of trabecular bone microarchitecture affects implant stability.* J Biomech, 2012. **45**(6): p. 1060-7.
14. Akagawa, Y., et al., *A mimic osseointegrated implant model for three-dimensional finite element analysis.* J Oral Rehabil, 2003. **30**(1): p. 41-5.
15. Vigolo, P., et al., *Clinical evaluation of small-diameter implants in single-tooth and multiple-implant restorations: a 7-year retrospective study.* Int J Oral Maxillofac Implants, 2004. **19**(5): p. 703-9.
16. Zinsli, B., et al., *Clinical evaluation of small-diameter ITI implants: a prospective study.* Int J Oral Maxillofac Implants, 2004. **19**(1): p. 92-9.
17. Garaicoa-Pazmino, C., et al., *Influence of crown/implant ratio on marginal bone loss: a systematic review.* J Periodontol, 2014. **85**(9): p. 1214-21.
18. Perelli, M., et al., *Short (5 and 7 mm long) porous implants in the posterior atrophic maxilla: a 5-year report of a prospective single-cohort study.* Eur J Oral Implantol, 2012. **5**(3): p. 265-72.
19. French, D., H. Larjava, and R. Ofec, *Retrospective cohort study of 4591 Straumann implants in private practice setting, with up to 10-year follow-up. Part 1: multivariate survival analysis.* Clin Oral Implants Res, 2014.
20. Rodrigo, D., et al., *Retrospective multicenter study of 230 6-mm SLA-surfaced implants with 1- to 6-year follow-up.* Int J Oral Maxillofac Implants, 2013. **28**(5): p. 1331-7.
21. Rossi, F., et al., *Early loading of 6-mm-short implants with a moderately rough surface supporting single crowns - a prospective 5-year cohort study.* Clin Oral Implants Res, 2014.
22. Srinivasan, M., et al., *Survival rates of short (6 mm) micro-rough surface implants: a review of literature and meta-analysis.* Clin Oral Implants Res, 2014. **25**(5): p. 539-45.
23. Lee, S.A., et al., *Systematic review and meta-analysis of randomized controlled trials for the management of limited vertical height in the posterior region: short implants (5 to 8 mm) vs longer implants (> 8 mm) in vertically augmented sites.* Int J Oral Maxillofac Implants, 2014. **29**(5): p. 1085-97.
24. Kennedy, K.S., et al., *A prospective clinical study to evaluate early success of short implants.* Int J Oral Maxillofac Implants, 2013. **28**(1): p. 170-7.
25. Huang, B., et al., *Influence of placement depth on bone remodeling around tapered internal connection implants: a histologic study in dogs.* Clin Oral Implants Res, 2014.
26. Strietzel, F.P., K. Neumann, and M. Hertel, *Impact of platform switching on marginal peri-*

implant bone-level changes. A systematic review and meta-analysis. Clin Oral Implants Res, 2014.
27. Mericske-Stern, R. and A. Worni, *Optimal number of oral implants for fixed reconstructions: a review of the literature.* Eur J Oral Implantol, 2014. **7 Suppl 2**: p. S133-53.
28. *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.* Jama, 2013. **310**(20): p. 2191-4.
29. *ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good Clinical Practice*.
30. Friberg, B., T. Jemt, and U. Lekholm, *Early failures in 4,641 consecutively placed Branemark dental implants: a study from stage 1 surgery to the connection of completed prostheses.* Int J Oral Maxillofac Implants, 1991. **6**(2): p. 142-6.
31. Bahat, O., *Treatment planning and placement of implants in the posterior maxillae: report of 732 consecutive Nobelpharma implants.* Int J Oral Maxillofac Implants, 1993. **8**(2): p. 151-61.
32. Naert, I., et al., *Biologic outcome of implant-supported restorations in the treatment of partial edentulism. part I: a longitudinal clinical evaluation.* Clin Oral Implants Res, 2002. **13**(4): p. 381-9.
33. Renouard, F. and D. Nisand, *Impact of implant length and diameter on survival rates.* Clin Oral Implants Res, 2006. **17 Suppl 2**: p. 35-51.
34. Neldam, C.A. and E.M. Pinholt, *State of the art of short dental implants: a systematic review of the literature.* Clin Implant Dent Relat Res, 2012. **14**(4): p. 622-32.
35. Misch, C.E., et al., *Implant success, survival, and failure: the International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference.* Implant Dent, 2008. **17**(1): p. 5-15.
36. Krebs, M., et al., *Long-Term Evaluation of ANKYLOS(R) Dental Implants, Part I: 20-Year Life Table Analysis of a Longitudinal Study of More Than 12,500 Implants.* Clin Implant Dent Relat Res, 2013.
37. Morris, H.F., et al., *AICRG, Part I: A 6-year multicentered, multidisciplinary clinical study of a new and innovative implant design.* J Oral Implantol, 2004. **30**(3): p. 125-33.
38. Rinke, S., et al., *Technical and biological complications of single-molar implant restorations.* Clin Oral Implants Res, 2014.
39. Yunus, N., et al., *Patient-based and clinical outcomes of implant telescopic attachment-retained mandibular overdentures: a 1-year longitudinal prospective study.* Int J Oral Maxillofac Implants, 2014. **29**(5): p. 1149-56.

Appendix A: CIP Signature pages
Signature page DENTSPLY Implants

Study Code: C-AN-14-001	**Version No:** Final V1.00
SPONSOR DENTSPLY IH AB Aminogatan 1 SE-431 21 Mölndal Sweden Phone No: +46 31 376 35 00	
I agree to the terms of this Clinical Investigation Plan.	
AnnaKarin Lundgren *Director Global Scientific Affairs* *Global Scientific Affairs*	150305 AnnaKarin Lundgren Date, Signature
Fredrik Ceder *Manager Clinical Research* *Global Scientific Affairs – Clinical Research*	150305 Fredrik Ceder Date, Signature
Anna Rydberg *Clinical Research Manager* *Global Scientific Affairs – Clinical Research*	15/MAR/2015 Anna Rydberg Date, Signature
This document contains confidential information, which should not be copied, referred to, released or published without written approval from DENTSPLY Implants. Investigators are cautioned that the information in this CIP may be subject to change and revision.	

Signature Page Investigator

Study Code: C-AN-14-001	**Version No:** Final V1.00	
Function in the study	International Coordinating Investigator Principal Investigator	☒ ☒
Name (full name, title)	Dr. Paul Weigl	
Study site No.	1	
Study site/ Institution name	J.W. Goethe-University Frankfurt am Main	
Contact details (address, phone)	Department of Postgraduate Education Faculty of Oral and Dental Medicine J.W. Goethe-University Frankfurt am Main Theodor-Stern-Kai 7, building # 29 60596 Frankfurt am Main Germany Phone: +49-69-6301-5729	

I agree to the terms of this Clinical Investigation Plan. I will conduct the study according to the procedures specified herein, and according to the principles of the Declaration of Helsinki, ISO 14155 and local regulations.

10. April 2015, _____

Date (DD/MMM/YYYY), Signature

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Dr. Paul Weigl
Faculty of Oral and Dental Medicine
Theodor-Stern-Kai 7, building # 29
60590 Frankfurt am Main
Phone: +49-69-6301-5731
E-Mail: weigl@em.uni-frankfurt.de

Signature Page Investigator

Study Code: C-AN-14-001		**Version No:** Final V1.00
Function in the study	International Coordinating Investigator	☐
	Principal Investigator	☒
Name (full name, title)	Prof. Wael Att	
Study site No.	2	
Study site/ Institution name	University of Freiburg	
Contact details (address, phone)	Department of Prosthodontics Hugstetter Str. 55 79106 Freiburg Germany Phone: +49 761 27047380	

I agree to the terms of this Clinical Investigation Plan. I will conduct the study according to the procedures specified herein, and according to the principles of the Declaration of Helsinki, ISO 14155 and local regulations.

30/03/2015

Date (DD/MMM/YYYY), Signature

Universitätsklinikum Freiburg
Department für Zahn-, Mund- u. Kieferheilkunde
Klinik für Zahnärztliche Prothetik
Ärztlicher Direktor:
Prof. Dr. Dr. h.c. J. R. Strub
Hugstetter Straße 55
D-79106 Freiburg

Signature Page Investigator

Study Code: C-AN-14-001	**Version No:** Final V1.00	
Function in the study	International Coordinating Investigator Principal Investigator	☐ ☒
Name (full name, title)	Dr. Theofilos Koutouzis	
Study site No.	3	
Study site/ Institution name	Nova Southeastern University	
Contact details (address, phone)	Nova Southeastern University Department of Periodontics NSU College of Dental Medicine 3200 South University Drive Fort Lauderdale FL 33328 USA Phone: +1 352 226 0730	

I agree to the terms of this Clinical Investigation Plan. I will conduct the study according to the procedures specified herein, and according to the principles of the Declaration of Helsinki, ISO 14155 and local regulations.

08/06/2015

Date (DD/MMM/YYYY), Signature

Appendix B: Visit and procedure plan

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9-14
	Screening and Inclusion	Pre-surgical planning	Implant Placement (IP)	Post-op Check	Abutment Surgery and Impression	Bite Registration	Try-in	Permanent Restoration (PR)	Follow-up
				IP+7-10 days	IP+13 weeks (±10 days)	IP+14 weeks (±5 days)	IP+16 weeks (±2 weeks)	IP+17 weeks (±2 weeks)	PR+6, 12, 24, 36, 48 and 60 months (±1 month)
Subject eligibility	X	X	X						
Written Informed Consent	X								
Subject demographics	X								
Oral examination	X								
CBCT		X	X						
OHIP		X						X	X[a]
Implant stability			X		X				
Clinical photos	X		X		X			X	X
Intraoral X-rays								X	X[b]
Plaque, PPD, BoP								X	X
AE documentation		X	X	X	X	X	X	X	X

[a] OHIP at Visit 10, 12 and 14

[b] Intraoral X-rays at Visit 10, 12 and 14

Appendix C: Dental chart

The two-digit-notation system as standardized by the Fédéderation Dentaire Internationale (F.D.I.) is used for the documentation.

FDI scheme

upper right								**upper left**							
18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
lower right								**lower left**							