Clinical Investigation Plan

Study code: C-OT-17-003

Study title: A prospective, multicenter study on Acuris™ - conometric concept for single tooth restoration. A 5-year follow-up study.

Investigational product(s): Conometric abutment, Conometric final cap.

Sponsor: DENTSPLY IH AB d.b.a. Dentsply Sirona Implants

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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
A prospective, multicenter study on Acuris™ - conometric concept for single tooth restoration. A 5-year follow-up study.

Sponsor
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International Co-ordinating Investigator
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Study site(s) and number of subjects planned

Anticipated number of study sites	9 sites
Anticipated number of subjects/implants	157 subjects/157 implants

Study period

Anticipated First Subject In (FSI)	2019 May
Anticipated Last Subject In (LSI)	2020 August
Anticipated Last Subject Out (LSO)	2025 September
Anticipated Data Base Lock (DBL)	2026 February

Indication
The Conometric Abutments are intended to be used together with all implant brands of Dentsply Sirona Implants; Ankylos, Astra Tech Implant System or Xive, for fixed friction retained single crown restorations.

Investigational product
Conometric abutment, Conometric final cap.

Primary objective(s)
Prosthetic survival 1 year after permanent restoration.

Study design
A prospective, non-controlled, multicentre study on the Acuris-conometric concept.

Subject population
Subjects, aged between 18-75 years, in need of single tooth replacement.

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

1. Subject aged between 18-75 years
2. Subject signed and dated the informed consent form
3. In need of an implant replacing a missing tooth in position 17 to 27 or 37 to 47, and each subject can only receive one study implant.
4. Neighbouring tooth to the planned implant must have
   - a natural root or an implant supported restoration mesially
   - a natural root or an implant supported restoration distally
   Exemption: If the planned implant is in the second molar position, an edentulous space is accepted distally.
5. Presence of natural tooth, partial prosthesis and/or implant supported restoration in the opposite jaw in contact with the planned crown
6. Deemed by the investigator as likely to present an initially stable implant situation

Exclusion criteria
Any of the following is regarded as a criterion for exclusion from the study (all criteria applies at study inclusion, but criteria numbered 1-5 also applies during the entire study period):

1. Unlikely to be able to comply with study procedures, according to Investigators judgement
2. Subject is not willing to participate in the study or not able to understand the content of the study
3. Unable or unwilling to return for follow-up visits for a period of five years
4. Involvement in the planning and conduct of the study
5. Simultaneous participation in another clinical study, or former participation in a clinical study during the last 6 months that may interfere with the present study
6. Previous enrolment in the present study
7. Severe non-compliance to CIP as judged by the Investigator and/or Dentsply Sirona Implants.
8. Uncontrolled pathological process in the oral cavity
9. Known or suspected current malignancy
10. History of radiation therapy in the head and neck region within 12 months prior to surgery
11. Systemic or local disease or condition that could compromise post-operative healing and/or osseointegration
12. Uncontrolled diabetes mellitus
13. Corticosteroids, iv bisphosphonates or any other medication that could influence post-operative healing and/or osseointegration
14. Current need for major bone grafting and/or augmentation in the planned implant area (minor grafting and soft tissue grafting are allowed)
15. Present alcohol and drug abuse
16. Smoking more than 10 cigarettes per day

Exclusion criteria at Visit 5 (Permanent Restoration)
17. Permanent restoration delivered later than 6 months after implant placement

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1 Introduction

1.1 Background

Acuris is developed for a conometric mode of retention for fixed implant restorations, based on friction. The crown is fixed for the patient, but removable for the clinician. The components are developed based on the already marketed Ankylos SynCone System and accessories, incl. Ankylos Welding Cap for SynCone 5°, and is available for all implant brands from Dentsply Sirona Implants (Ankylos, Astra Tech Implant System and Xive).

Advantages of Acuris is quick placement of the final crown, which leads to time-saving for both the clinician and the patient, as well as a streamlined procedure. This is a fixed retention intended not to be removed unless absolutely necessary. However, the crown can easily be removed, e.g. for repair, adjustments or better access for necessary treatment, if needed. According to the Instruction For Use (IFU) the crown can be removed and reattached ten times. There is no prosthetic screw used, which might improve esthetics, due to no visible screw access holes. No cement is used for retention, and therefore there is no risk of biological complications due to excess cement.

1.1.1 Pre-clinical experience

Experimental studies report on different aspects of Acuris; including evaluation of the conometric mode of retention over time under dynamic loading[1], the retention of the conical connection between cap and abutment loaded with dynamic lateral forces after an initial axial load[2] as well as the retention between cap and abutment, preloaded with different axial loads[3]. These studies show that the conometric connection of the tested samples maintain its stability over time under cyclic loading, with no effect of wear detected[1]. After dynamic lateral loading, all caps showed sufficient retention to the abutment and no cap was separated from the abutment during the tests[3].

1.1.2 Clinical experience

Conometric retention, with the use of the conic coupling abutments for fixed prostheses (fixed for the patient, removable for the clinician), has been described in a number of clinical studies[4-9] including over 450 implants in over 200 patients. They cover full and partial prosthesis, placement in the mandible and maxilla, applying conventional and immediate loading protocols in extraction sockets and healed ridges, with up to 5 years of follow-up. No disconnection of any prosthesis has been reported.

The clinical use of the SynCone abutment system including Ankylos Welding Cap for SynCone 5° is also well documented. With up to 6 years of follow-up, long term reliable retention has been reported for complete overdentures when placed in the mandible, maxilla, healed sites, extraction sockets, and when applying immediate loading[10-13].

The present study is designed to obtain scientific clinical data to demonstrate long-term success of the conometric concept, Acuris, for single tooth restorations.

1.2 Study rationale

The clinical study is designed as a Post Market Clinical Follow-up study to provide information on clinical performance using the newly developed Acuris-conometric concept for single tooth restorations, as a new friction mode of retention for seating the abutment without using cement or screws.

The conometric abutment is developed for use with all implant brands from Dentsply Sirona

Implants (Ankylos, Astra Tech Implant System, Xive), and are used together with the conometric retention caps as retentive part of the restoration. The design for the retentive part of the abutments is similar for all implant brands to enable use of the same cap irrespective of implant system.

1.3 Risk/ benefit assessment

There are no obvious risks for the subjects participating in this study. There is a possibility that the new conometric retention mode might lead to technical and biological complications in a short or long-term performance. No unexpected complications beside general complications related to prosthetic restorations are being expected.

No additional x-rays compared to regular implant treatment will be taken. All attempts to limit x-ray exposure will be made during the study, including proper shielding. A benefit of taking x-rays, is the possibility to discover pathological processes at an early stage. The study subjects will benefit from careful examination and follow-up during the study participation.

2 Study objectives

2.1 Primary objective

Primary objective	Corresponding primary outcome variable
Evaluate prosthetic survival 1 year after permanent restoration	Prosthetic survival will be categorized as No/Yes. It will be categorized as 'Yes' if **all** of the following criteria is fulfilled: ▪ permanent restoration is remaining in situ ▪ no loss of conometric retention between abutment and final cap ▪ no fracture of abutment ▪ no loss of abutment

2.2 Secondary objectives

Secondary objectives	Corresponding secondary outcome variables
Evaluate prosthetic survival 3 and 5 years after permanent restoration	Prosthetic survival will be categorized as No/Yes (see Primary objective)
Evaluate implant survival rate up to 5 years after permanent restoration.	Implant survival will be evaluated clinically and radiographically
Evaluate maintenance of marginal bone levels up to 5 years after permanent restoration.	Marginal Bone Levels and alterations
Evaluate condition of the peri-implant mucosa up to 5 years after permanent restoration.	Bleeding on Probing, Probing Pocket Depth and Plaque

2.3 Safety objectives

Safety objectives	Corresponding safety outcome variables
Evaluate Adverse Events (AE) and Adverse Device Effects (ADE)	Number and severity of AE/ADE at each study visit.

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 Clinical Study Agreements (CSAs) 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 given a favorable opinion in writing/approval by an IEC/IRB or Regulatory Authority 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 Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs) and Device Deficiencies with SADE potential will be provided to the IEC/IRB and/ or Regulatory Authorities according to local regulations and guidelines.

Dentsply Sirona Implants will provide Principal Investigators (PIs) 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[14] and are consistent with ISO 14155[15] and applicable regulatory requirements.

Dentsply Sirona Implants and the Investigator are obliged to take over the responsibilities specified for both roles in the current ISO 14155.

3.3 Informed consent

The Informed Consent Form (ICF) must be approved by the responsible IEC/IRB prior to the study start.

The PI 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 PI 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 PI 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 Sirona 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 stored in the study data base and/or processed by the data manager and Dentsply Sirona Implants will be 'pseudonymized' and is identified by the study code and the subject identification number. The ICF will also explain that for data verification purposes, authorized representatives of Dentsply Sirona Implants, a regulatory authority and/or an IEC/IRB may require direct access to parts of the hospital or practice records relevant to the study, including subject's medical history. The only information revealing the connection between subjects' real identity and study subject number will be stored securely at the respective study site.

3.5 Insurance

Subjects participating in this clinical study are insured by Dentsply Sirona Implants, provided that the CIP and other written procedures are followed. For further details, see the CSA.

4 Study design

4.1 Overall study design

A prospective, non-controlled, multicentre study on the Acuris-conometric concept. The study comprises a 5 year follow-up from baseline, permanent restoration, and includes 11 visits. Each subject will receive one single implant placed in position 17-27 or 37-47 to support a single restoration. The implant will be placed in fresh extraction socket or healed ridge using one- or two-stage surgical protocol, immediate or conventional loading. The permanent restoration must be in place within six months after implant surgery at the latest. A conometric abutment will be used for the prosthetic restoration. The final crown will be cemented onto the final cap extra-orally and fixated on the conometric abutment using retention mode.

The sample size estimation shows that 133 fully evaluable subjects are needed to fulfill the primary objective. Given an assumed drop-out rate of 15 % the aim is to include 157 subjects in total, see section 10.4 "Determination of sample size" for details.

However, if the drop-out rate is lower or higher than the estimated level, the number of enrolled subjects may be adjusted in order to reach the 133 fully evaluable subjects.

It is expected that the study will include 9 study sites and that each study site will enroll approximately 15-20 subjects using the Acuris-conometric concept on the implant systems; Ankylos, Astra Tech Implant System or Xive. Each site will use only one implant system.

The overall study design is presented in Appendix B: Visit and procedure plan.

4.1.1 Study duration

Anticipated FSI: 2019 May
Anticipated LSI: 2020 August
Anticipated LSO: 2025 September
Anticipated DBL: 2026 February

4.2 Choice of outcome variables and study population

4.2.1 Choice of outcome variable

Prosthetic survival is chosen as primary objective to show that the Acuris-conometric concept has performed according to expectations during the study, since this is a new mode of retention using friction for seating the crown of single tooth restorations without using cement or screws.

4.2.2 Choice of study population

Subjects in need of single tooth replacement have been chosen, since this is the target subject population for treatment with the Acuris-conometric concept.

5 Study procedures

5.1 Visits

The pseudonymized subject data, investigation results and procedures during the treatment phase as well as safety information 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.

Additional visits may be scheduled at the discretion of the investigator recorded as extra visits in the eCRF.

The Fédéderation Dentaire Internationale (F.D.I.) will be used, see Appendix C: Dental chart.

Pre-screening activity (outside study) – Investigator or delegate may identify potentially suitable study subjects by e.g. a database search, when seeing patients at regular dental appointments at the clinic or evaluating referrals. If possible, an unbiased discussion on available treatment options, and an initial review of certain predefined selection criteria could be performed.

Throughout the study, the guidelines in the following manuals should be followed:

- Surgical manual Ankylos (32671086-USX-1804)
- Surgical manual Astra Tech Implant System (32671181-USX-1804)
- Surgical manual Xive (32670050-USX-1810)
- Acuris-conometric concept, Manual and product catalog Ankylos (32671509-USX-1808)
- Acuris-conometric concept, Manual and product catalog Astra Tech Implant System (32671510-USX-1810)
- Acuris-conometric concept, Manual and product catalog Xive (32671511-USX-1812)
- Clinical Photography Manual (32671374-USX-1708)

Clinical photographs should be taken for at least 5 subjects selected by each study site. Clinical photographs can be used in future case presentations, scientific publications etc.

Radiographs and clinical photographs obtained during the study will be uploaded into the eCRF by the Investigator.

5.1.1 Visit 1 Screening and pre-surgical planning

Subjects in need of a single implant restoration will be screened and considered for treatment in the study. Only one implant per subject will be included within the study. Subjects fulfilling all of the Inclusion criteria and none of the Exclusion criteria, are considered eligible for participating

in the study. Clinical photographs will be taken (at least 5 subjects).

5.1.1.1 Written informed consent

If the subject is eligible, 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 Informed consent).

5.1.1.2 Pre-operative planning

Treatment considerations for implant subjects should include an evaluation of:

- Oral health status (incl. periodontal status and restorative status)
- Medical status (anamnesis)
- Risk factors

During pre-operative planning it is important to check that the height and width of the jawbone is sufficient for placement of the implant. Bone quality and quantity, expected primary implant stability, design of restoration and loading conditions should always be carefully examined and assessed by the clinician when determining time to loading of the implant.

The screening procedure will include collection of demographic data, see section 6.2 “Demographics and other baseline characteristics”. Pre-surgical planning should follow the guidelines described in applicable surgical manual. This procedure will include a clinical and radiographical examination, e.g. panoramic, intra-oral or Cone Beam Computed Tomography (CBCT). Pre-existing radiographs deemed by the investigator as being insufficient to assess subject eligibility or being older than six months, will prompt a new radiographic examination.

5.1.2 Visit 2 Implant Placement (IP)

Subjects meeting all of the inclusion and none of the exclusion criteria will be treated according to the study protocol. Subjects not fulfilling the criteria will be terminated from the study and will receive an appropriate treatment and thereafter followed according to the clinic’s standard practice. The subject will receive antibiotic prophylaxis according to local practice and a prescription for post-surgical chlorhexidine rinse (twice daily for 10 days). Other pre-surgical, surgical and post-surgical care will be given at the discretion of the investigator and recorded in appropriate sections in the eCRF.

Pre-surgical radiographic findings of bone quality and quantity (Lekholm and Zarb[16]) from visit 1, will be determined during surgery and recorded in eCRF. Primary implant stability will be examined manually by the investigator and recorded as “Yes/No” in the eCRF. If needed, minor grafting and soft tissue grafting may be performed. Intraoral radiographs will be obtained. Clinical photographs will be taken (at least 5 subjects). All types of safety events (6.4.1 Types of safety events) will be recorded.

Each study site will use their assigned implant system; Ankylos, Astra Tech Implant System or Xive, and must follow the guidelines described in applicable manuals[(a-f)].

The implant can be placed in a healed ridge or in a fresh extraction socket.

During the surgery, based on the quality of supporting bone and the initial stability of the implant, the investigator will determine the final treatment approach, i.e.:

- One- or two-stage surgical procedure
- Immediate or conventional loading protocol

Prepare the implant site and install the implant. At implant installation, decide one of the following approaches:

1. The use of cover screw
2. The use of healing abutment/gingiva former

3. The use of Conometric Abutment, Conometric Temporization Cap and Temporary crown (immediate temporization)
4. The use of Conometric Abutment and Conometric Healing Cap

Applicable for choice 3 and 4:

- Measure the soft tissue height. It is preferable to place the abutment margin 1 mm below he soft tissue margin. Select the appropriate conometric abutment with regard to height and angulation. Use applicable instruments for the installation and assure tightening at recommended torque for each implant brand.
- Make sure to record the reference number and lot number of the conometric abutment in eCRF for each subject, mark the package with applicable subject ID and keep at the clinic.
- When immediate loading is selected, the Conometric Temporization Cap is used for temporary restoration. It is important to avoid interference from the mucosa surrounding the abutment. Ensure sufficient space for the final restoration by designing the temporary crown in a way that allow the mucosa to heal in a suitable shape.
- When a temporary crown is not needed an alternative is to use a Conometric Healing Cap which will be snapped onto the abutment.

a) Surgical manual Ankylos (32671086-USX-1804)
b) Surgical manual Astra Tech Implant System (32671181-USX-1804)
c) Surgical manual Xive (32670050-USX-1810)
d) Acuris-conometric concept, Manual and product catalog Ankylos (32671509-USX-1808)
e) Acuris-conometric concept, Manual and product catalog Astra Tech Implant System (32671510-USX-1810)
f) Acuris-conometric concept, Manual and product catalog Xive (32671511-USX-1812)

5.1.3 Visit 3 (IP + 1-2 weeks)

One to two weeks after implant placement the subject will return for clinical examination of the implant/abutment and the healing process. Any sutures will be removed and the subject will be given oral hygiene instructions. All types of safety events will be recorded.

5.1.4 Visit 4 Impression (IP + max 5 ½ months)

The subject will return to the clinic for impression taking no later than 5 ½ months after surgery, depending of the loading protocol.

NB: Schedule the impression visit so that the final crown can be produced and delivered within 6 months after implant placement.

Implant stability will be examined manually. If no pain or mobility is present, impressions will be taken for fabrication of the final crown.

The impression will be made on conometric abutment level, following the guidelines described in applicable Acuris-conometric concept Manual and product catalog[d-f].

- If a healing abutment/gingiva former or a cover screw was placed, unscrew and install the appropriate Conometric abutment before the impression taking.
- If a Conometric Temporary Crown or a Conometric Healing Cap is in place, remove these before impression taking.
- Align the Conometric Impression Cap with the indexing part of the abutment and seat it firmly, allowing it to snap into place.
- Take the impression using a closed tray impression technique.
- Reinstall the Conometric Temporary Crown or reinstall/install the Conometric Healing Cap.
- Send the impression together with a Conometric Final Cap to the laboratory for fabrication of the final crown. Before sending the package, record the reference and lot number of the Conometric Final Cap in eCRF and mark the package with applicable subject ID.
- Lab produces the final ceramic crown (all ceramic; e.g. lithium disilicate, Zirconia), using the Conometric Analog and the Conometric Lab Cap, and cements the final crown onto the

Conometric Final Cap.
- Lab sends the final crown, together with the empty package, to the clinic.
- The package must be stored at the clinic in order to track the Investigational Product.

Clinical photographs will be taken (at least 5 subjects). All types of safety events will be recorded.

5.1.5 Visit 5 Permanent Restoration (PR) (IP + max 6 months)

The permanent restoration must be in place within six months after implant placement, following the procedures described in Acuris-conometric concept Manual and product catalog[d-f]. Implant stability will be examined manually. A clinical examination evaluating the periimplant mucosa (Probing Pocket Depth (PPD) and Bleeding on Probing (BoP)) will be performed. Oral hygiene instruction will be given if needed. Intraoral radiographs will be obtained. Clinical photographs will be taken (at least 5 subjects). All types of safety events will be recorded.

- Remove the Conometric Temporary Crown or Conometric Healing Cap.
- Select a suitable single-use tip and attach to the Conometric Fixation Tool depending on the crown form.
- Place the final crown aligned with the index on the abutment.
- Check occlusion and contact points.
- If needed, remove the crown for correction and polishing, and then reinsert the crown aligned with the index on the abutment.
- Press the Conometric Fixation Tool towards the crown to activate the friction retention between Conometric Final Cap/final crown and abutment. An audible click occurs when the spring is released and activates the retention.
- Check retention manually.

5.1.6 Visit 6-11 Follow-up (PR + 6 months, 1, 2, 3, 4, 5 years) (± 1 month)

The subject will return for follow-up visits at 6 months, 1, 2, 3, 4 and 5 years after permanent restoration. At all follow-up visits a clinical examination evaluating the presence of plaque and the condition of periimplant mucosa (PPD and BoP) will be performed. Plaque will be recorded as presence of plaque by visual inspection on four surfaces at each implant site. If a high presence of plaque is noted the subject should be re-instructed concerning oral hygiene. Intra-oral radiographs will be taken at 1, 3 and 5 year follow-up visits. Clinical photographs will be taken at 1, 3 and 5 year follow-up visits (at least 5 subjects). All types of safety events will be recorded at all follow-up visits.

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

Subjects, aged between 18-75 years, in need of single tooth replacement will be screened and considered for implant treatment in the study. Only one implant per subject will be included within the study.

5.3.1 Selection records

The Investigator(s) must keep a Screening Log of subjects who were considered for enrollment. Subjects listed on the log are either enrolled or failed to fulfill inclusion-/exclusion criteria, so called 'Screening failures'.

This information is necessary to establish to assure 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 not be collected or copied by Dentsply Sirona 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. Subject aged between 18-75 years
2. Subject signed and dated the informed consent form
3. In need of an implant replacing a missing tooth in position 17 to 27 or 37 to 47, and each subject can only receive one study implant.
4. Neighbouring tooth to the planned implant must have
   - a natural root or an implant supported restoration mesially
   - a natural root or an implant supported restoration distally
   Exemption: If the planned implant is in the second molar position, an edentulous space is accepted distally.
5. Presence of natural tooth, partial prosthesis and/or implant supported restoration in the opposite jaw in contact with the planned crown
6. Deemed by the investigator as likely to present an initially stable implant situation

5.3.3.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study (all criteria applies at study inclusion, but criteria numbered 1-5 also applies during the entire study period):

1. Unlikely to be able to comply with study procedures, according to Investigators judgement
2. Subject is not willing to participate in the study or not able to understand the content of the study
3. Involvement in the planning and conduct of the study
4. Severe non-compliance to CIP as judged by the Investigator and/or Dentsply Sirona Implants.
5. Unable or unwilling to return for follow-up visits for a period of five years
6. Simultaneous participation in another clinical study, or former participation in a clinical study during the last 6 months that may interfere with the present study
7. Previous enrolment in the present study
8. Uncontrolled pathological process in the oral cavity
9. Known or suspected current malignancy
10. History of radiation therapy in the head and neck region within 12 months prior to surgery
11. Systemic or local disease or condition that could compromise post-operative healing and/or osseointegration
12. Uncontrolled diabetes mellitus

13. Corticosteroids, iv bisphosphonates or any other medication that could influence post-operative healing and/or osseointegration
14. Current need for major bone grafting and/or augmentation in the planned implant area (minor grafting and soft tissue grafting are allowed)
15. Present alcohol and drug abuse
16. Smoking more than 10 cigarettes per day

Exclusion criteria at Visit 5 (Permanent Restoration)

17. Permanent restoration delivered later than 6 months after implant placement

5.4 Restrictions

To avoid excessive loading of the implant during the healing period the subject should be informed to avoid food difficult to chew from implant placement to delivery of permanent prosthetic restoration according to the dentist judgement.

If the subject is a smoker, smoking should be limited to a maximum of 10 cigarettes per day.

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 may include:

- Voluntary discontinuation by the subject who is free to at any time discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reasons as judged by the Investigator or Dentsply Sirona Implants.
- Severe non-compliance to the CIP as judged by the Investigator and/or Dentsply Sirona Implants.
- Incorrect enrollment, i.e. a subject did not to meet the required inclusion/exclusion criteria for the study, but nevertheless was enrolled (see section 5.3.3 Subject-selection criteria).
- 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, e-mail or letter; all should be documented in the subject's medical records).
- Loss of the study implant. (If a new implant is placed, the new implant should not be recorded in the eCRF.)
- Subjects in need of replacement of existing Investigational Product (IP) (abutment or final cap) after Permanent Restoration (PR).
  - Removal of existing IP after PR for adjustments (e.g. maintenance, polish, esthetic adjustments of crown) is not reason for discontinuation.
  - A loose abutment screw, is not reason for discontinuation if replacement of the abutment screw is possible without changing the abutment.

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 CRF should be completed. Safety events should be followed up. Any study specific material provided to the subject should be collected.

The reimbursement of the treatment will be reduced as described in the CSA, as applicable.

Removed Investigational Products will be returned to Dentsply Sirona Implants for further investigation.

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 records. The subject should be discontinued and no follow-up is necessary from a study perspective.

If a subject has been enrolled and study-related surgery started, but for any reason no Investigational Product (IP) could be inserted (e.g. not enough bone according to inclusion/exclusion criteria), the Investigator must document this in the subject records. The subject should be discontinued and no follow-up is necessary from a study perspective. However the subject should be treated according to standard practice.

If a subject has been enrolled and received the IP, although the inclusion/ exclusion criteria are violated, the subject will continue in the study, but will not be part of the Per Protocol (PP) analysis.

If a subject will not receive the permanent restoration within 6 months after implant placement, the subject will discontinue the study (not eligible according to Inclusion criteria no. 17) and no follow-up is necessary from a study perspective.

- If a subject lose the study implant (implant failure) *before* the permanent restoration is in place, the subject will discontinue the study and no follow-up is necessary from a study perspective.

6 Study methodology

6.1 Prior and concomitant treatment(s)

Systemic corticosteroids, iv bisphosphonates or any other medication that could compromise post-operative healing and/or osseointegration should be avoided during the study period.

Subjects requiring sedation or general anesthesia before the operation will receive this in accordance with the clinic's normal routine.

Antibiotic prophylaxis will be given according to the clinic´s normal routine.

After surgery, mouth rinsing with chlorhexidine 0.10 or 0.12 %, twice daily for 10 days will be prescribed. If necessary, as deemed by the investigator, this period can be prolonged.

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). Details of all medication (including analgesics, sedation and antibiotics) will be recorded in the eCRF on the medication page.

For prohibited medication, see 5.3.3.2 Exclusion criteria.

6.2 Demographics and other baseline characteristics

- Date of birth
- Gender
- Relevant medical and surgical history

- Concurrent medication
- Oral examination
- Status of dentition
- Smoking status
- Implant, abutment and crown details
- Bone quantity and quality
- Surgical approach (one- or two-stage surgery, healed site, extraction socket)
- Implant stability
- Loading regimen
- Temporary restoration
- Impression details
- Permanent restoration

6.3 Assessments of outcome variables

One implant per subject will be placed within the study. Implant and subject level will be equivalent, and from hereon it will be stated implant level.

6.3.1 Primary outcome variable

6.3.1.1 Prosthetic survival 1 year after permanent restoration

Prosthetic survival will be determined by evaluating presence of original permanent restoration, remained retention between abutment and final cap, and occurrence of fracture/loss of abutment.

6.3.1.2 Assessment of primary outcome variable

Prosthetic survival will be categorized as No/Yes.

It will be categorized as ‘Yes’ if **all** of the following criteria is fulfilled:

- permanent restoration is remaining in situ
- no loss of conometric retention between abutment and final cap
- no fracture of abutment
- no loss of abutment

It will be categorized as ‘No’ if **any** of the following is fulfilled:

- permanent restoration not in situ
- loss of conometric retention between abutment and final cap
- fracture of abutment
- loss of abutment

6.3.2 Secondary outcome variables

6.3.2.1 Prosthetic survival 3 and up 5 year after permanent restoration

Prosthetic survival will be determined by evaluating presence of original permanent restoration, remained retention between abutment and final cap, and occurrence of fracture/loss of abutment.

6.3.2.1.1 Assessment of prosthetic survival 3 and 5 year after permanent restoration

Prosthetic survival will be categorized as No/Yes (see Assessment of primary outcome variable).

6.3.2.2 Implant survival

Implant survival rate up to five years after permanent restoration (number of implants in situ). Any implant that is removed or lost after permanent restoration will be considered an implant loss, whatever the reason for removal.

6.3.2.2.1 Assessment of Implant survival

Implant survival will be categorized as success (No/Yes)

Number of remaining implants counted clinically and radiographically, i.e. 'Yes' or 'No' for each implant where 'Yes' means that the implant is still remaining in situ and 'No' means that the implant is not in situ. Implant survival rate will be analyzed on an implant level, i.e. proportion survived implants.

6.3.2.3 Marginal Bone Levels

Marginal bone levels will be determined from the radiographs, expressed as the distance from the implant reference point to the most coronal bone-to-implant contact on the mesial and distal side of the implant.

6.3.2.3.1 Assessment of marginal bone levels

Intraoral radiographs will be used to assess marginal bone levels. To ensure reproducibility between the examinations, radiographs will be taken with parallel technique using film holders, whenever possible. 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. Peri-implant radiolucency will be recorded as present or absent. 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. Distances from a reference point on the implant to the most coronal bone-to-implant contact on the mesial and distal aspect of the implant will be recorded. All radiographs will be evaluated by a radiologist independent from the investigational group.

6.3.2.4 Condition of periimplant mucosa

Condition of periimplant mucosa will be measured by assessing of Probing Pocket Depth (PPD) and Bleeding on Probing (BoP). Presence of plaque will be recorded.

6.3.2.4.1 Assessment of periimplant mucosa

PPD and BoP will be evaluated at four surfaces around the implant (mesial, distal, buccal and lingual), 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. Bleeding will be recorded as presence or absence of bleeding when probing to the bottom of the pocket. Plaque will be recorded as presence or absence of plaque by visual inspection on four surfaces at each implant site.

For PPD mean values will be calculated for each implant. Changes over time will be analyzed. The proportion of surfaces that shows presence of bleeding when measuring probing pocket depth will be calculated and presented on an implant level for each visit. Changes over time will be analyzed.

For plaque the proportion of surfaces with presence of plaque will be calculated and presented on an implant level for each visit. Changes over time will be analyzed.

6.4 Safety definitions and reporting

6.4.1 Types of safety events

An overview of the different types of AEs can be found in 6.4.1 Types of safety events.

6.4.1.1 Adverse Event (AE)

An AE is any untoward medical 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 (IP) or the procedures involved. For users or other persons, this definition is restricted to events related to the IP.

All safety events involving subjects start as an AE, but might be further defined as ADE, SAE or SADE depending of the severity of the complication, or if judged as related to the medical device or procedure.

6.4.1.2 Adverse Device Effect (ADE)

An ADE is an AE related to the use of the medical device, i.e. not only the Investigational Product (IP), but also other medical devices used in the study, e.g. implants, conometric temporization cap and other prosthetic parts.

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

6.4.1.3 Serious Adverse Event (SAE)

An SAE is an AE that:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization *(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 foetal distress, foetal 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 a SAE.

6.4.1.5 Device Deficiency (DD)

A DD is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labeling. A DD is an event associated with the product itself, not with the subject.

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

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

6.4.2 AE and ADE reporting

In clinical studies, an AE can include an untoward medical condition 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
- Medical 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, and must be recorded in eCRF.

If an AE/ADE results in a subject's discontinuation in the study, this should be recorded at the Study Termination page in the eCRF. Not only the Investigational Product (IP), but also other medical devices used in the study, e.g. implants, conometric temporization cap and other 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, screw fracture, loss of retention, at study position.

6.4.3 SAE and SADE reporting

SAEs and SADEs must be reported to Dentsply Sirona Implants as soon as the Investigator becomes aware of it.

Dentsply Sirona Implants and the Investigators will distinguish between SAEs related to the medical device and those related to the procedures (any procedure specific to the clinical investigation). An SAE can be related both to procedures and the Investigational Product (IP).

For SAEs and 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 Sirona Implants.
- Follow up the initial SAE/SADE information as soon as new information is available.
- Report to the IEC/IRB any SAEs/SADEs, as per local requirements *(in multicentre investigations this may include the SAEs/SADEs reported from another site, this information will be provided by Dentsply Sirona Implants, if required).*
- Report to Regulatory Authorities any SAEs/SADEs, as per local requirements *(in multicentre investigations this may include the SAEs/SADEs reported from another site, this information will be provided by Dentsply Sirona Implants, if required).*
- Provide Dentsply Sirona Implants with all SAE/SADE related documentation and correspondence to the IEC/IRB and/or Regulatory Authority.

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

6.4.4 Device Deficiency reporting

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

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

For device deficiencies that fulfil the SADE definition the Investigator must provide Dentsply Sirona Implants with additional information.

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 CRF and, in accordance to the reporting requirements described above.

If it is suspected that the medical device under investigation may have interfered with the effectiveness of a contraceptive medication/device, this should be reported as an ADE. Pregnancy itself, or elective abortions without complications, should not be reported as AEs.

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 CRF.

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 Sirona 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 Sirona 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 Sirona Implants and the study site's IEC/IRB must be notified. Approval of the revised ICF by Dentsply Sirona Implants and by the IEC/IRB is required before the revised form is used. Dentsply Sirona Implants will distribute amendments and new versions of the CIP to each PI(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 Sirona Implants will visit the 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 Sirona Implants or its representatives.

During the course of the study, a study monitor from Dentsply Sirona 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 CRFs, and that Investigational Product (IP) accountability checks are being

performed
- Perform source data verification (a comparison of the data in the CRFs 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 Sirona 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 Sirona 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 Sirona 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 Sirona Implants immediately if contacted by a regulatory agency about an inspection at his or her site.

7.4 Training of study site staff

The PI 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.

Before the first subject is entered into the study, the study staff will be trained to use the EDC system by Dentsply Sirona 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 Sirona Implants and the IEC/IRB. Furthermore, such deviations shall be documented and reported as soon as possible to Dentsply Sirona Implants and the IEC/IRB.

All CIP deviations must be directly reported to the Study Team Leader, by either the Investigator or Monitor. The further procedure of CIP deviation handling, with special focus on the effect on the data analysis is described in section 10.2 Description of analysis sets.

Should the Investigator break any obligations under the CIP or CSA and fail to remedy such a breach where it is capable of cure, Dentsply Sirona Implants retains the right to disqualify the study site from further study participation.

7.6 Study agreements

The PI at the 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 Sirona Implants and the PI 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 Sirona 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 (IP).

7.8 Publication policy

Results from 1, 3 and 5-year data are planned to be compiled into e.g. manuscripts for submission to peer-reviewed scientific journals, poster presentations, oral presentations etc.

The data will be provided by Dentsply Sirona Implants and the writing process will be coordinated by the International Coordinating Investigator.

For authorship, see CSA.

8 Investigational Products (IPs)

Investigational Products are the Conometric Abutment and the Conometric Final Cap. Additional products are described below.

Investigational Products – for Ankylos	
Product name	Conometric Abutment
Diameter	3.3, 4.5 mm
Heights	1.5, 3.0, 4,5 mm
Characteristics	Straight or Angled 15°, Titanium Alloy-ELI Straight 3.3 mm is an one-piece abutment
Product name	Conometric Final Cap
Diameter	4.6, 5.8 mm
Heights	5 mm
Characteristics	Titanium grade 4, TiN-coated
Additional Products – for Ankylos	
Product name	Ankylos C/X
Diameter	3.5, 4.5, 5.5, 7.0 mm
Lengths	6.6-17 mm
Characteristics	Dental implants
Product name	Conometric Healing Cap
Diameter	4.8, 6.0 mm
Heights	5.3 mm
Characteristics	PEEK

Product name	Conometric Temporization Cap
Diameter	4.6, 5.8 mm
Heights	5, 5.3 mm
Characteristics	Titanium Alloy-ELI/PEEK or PEEK

Investigational Products – for Astra Tech Implant System

Product name	Conometric Abutment
Diameter	3.3, 4.5 mm
Heights	1.0, 2.0, 3.0 mm
Characteristics	Straight or Angled 15°, Titanium Alloy-ELI Straight 3.3 mm is an one-piece abutment

Product name	Conometric Final Cap
Diameter	4.6, 5.8 mm
Heights	5.0 mm
Characteristics	Titanium grade 4, TiN-coated

Additional Products – for Astra Tech Implant System

Diameter	3.6 S, 4.2 S, 4.2 C mm
Lengths	6-17 mm
Characteristics	Dental implants

Product name	Conometric Healing Cap
Diameter	4.8, 6.0 mm
Heights	5.3 mm
Characteristics	PEEK

Product name	Conometric Temporization Cap
Diameter	4.6, 5.8 mm
Heights	5.0, 5.3 mm
Characteristics	Titanium Alloy-ELI/PEEK or PEEK

Investigational Products – for Xive

Product name	Conometric Abutment
Diameter	4.5 mm
Heights	1.0, 2.0, 3.0. mm
Characteristics	Straight or Angled 15°, Titanium Alloy-ELI

Product name	Conometric Final Cap
Diameter	5.8 mm
Heights	5.0 mm
Characteristics	Titanium grade 4, TiN-coated

Additional Products – for Xive	
Product name	Xive S plus
Diameter	3.4, 3.8 mm
Lengths	8-18 mm
Characteristics	Dental implants
Product name	Conometric Healing Cap
Diameter	6.0 mm
Heights	5.3 mm
Characteristics	PEEK
Product name	Conometric Temporization Cap
Diameter	5.8 mm
Heights	5.3 mm
Characteristics	PEEK

8.1 Indications for use

The investigational products listed above are to be used in accordance with the Acuris – conometric concept for Dentsply Sirona implant systems; Ankylos, Astra Tech Implant System and Xive, i.e. an implant-prosthetic procedure for the restoration of single-tooth implants. The Conometric Abutments are intended to be used for fixed friction retained single crowns. Applicable Manuals for each category of investigational products and corresponding procedures shall be followed (manuals listed continuously in the text in the sequence they appear in the treatment flow).

8.2 Labeling

The packing and labeling of the Investigational Product will be performed by Dentsply Sirona Implants in accordance with GMP (Good Manufacturing Practice). The Labeling of the investigational product will also be carried out by Dentsply Sirona Implants in accordance ISO 14155. The labels will be available in English language and in accordance with local regulations.

In addition, study products will be labeled as follows:

- C-OT-17-003
- Name and address of Principal Investigator
- A separate label with text, according to national law in the country where the study is conducted, with the following sentence translated into local languages: “Only for clinical research”.

8.3 Storage and accountability records

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

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

9 Data collection and data management

9.1 Case Report Form recording and processing

Study data will be entered into electronic Case Report Forms (eCRFs) using Viedoc™, a web based Electronic Data Capture (EDC) system. Viedoc is compliant with good practices and regulatory requirements for clinical trials issued by e.g. FDA, EMA and PMDA. Trained and authorized study site personnel will be responsible for entering the study data into Viedoc. Data entered into Viedoc will be immediately saved to a central database, hosted by a 3rd party, PCG Solutions AB. Instructions for handling the system and filling in the eCRF e.g. how to log on, navigate and signing of data is found in the Investigator's Manual.

Dentsply Sirona Implants will review entered data, verify source data and lock data to prevent further editing. If not already done, the PI will be prompted to sign the eCRF electronically. A contemporaneous copy of the CRF will be available for the study site in Viedoc.

Data queries will be raised for inconsistent, missing, unclear or questionable data. The study site personnel is required to resolve any such queries. All entries in the study database will be available in an audit trail. When data is complete and 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 durable media e.g CD-ROM or DVD to be archived in the ISF at the study site after clean file. The copies will be created by trained study site personnel. Dentsply Sirona Implants will not at any time point be in control of the eCRF data archived in the ISF, unless the copy is sealed by 3rd party and then only for the purpose of delivering it to the study site.

Dentsply Sirona Implants will assume responsibility for the long-term storage of all data in compliance with the applicable local laws and ISO 14155. Study data will be securely stored at Dentsply Sirona Implants, with restricted access. Data will be retained by Dentsply Sirona Implants at least 15 years after this study has ended, or at least 15 years after the investigational devices are no longer available on any market, whichever is the longest.

10 Statistical methods and data analysis

10.1 Statistical evaluation – general aspects

A separate Statistical Analysis Plan may be prepared before database lock 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 and p-values may be complemented by confidence intervals as appropriate.

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 consideration to any covariates or prognostic factors will be taken in the statistical analysis.

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 Determination of sample size. Dropouts will be analyzed as described in Section 10.2 Description of analysis sets.

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 a Per Protocol (PP) population approach. The S analysis set will consist of all enrolled subjects where any safety parameters, study specific procedures or study specific measures were performed and/or collected. Safety events will be divided and presented as two different groups depending on when the safety event started:

1. Pre-Permanent Restoration delivery: Safety events with start date prior to Permanent Restoration i.e. the period from Implant installation up to Permanent Restoration delivery date.
2. Post permanent delivery: Safety events with start date same as or after Permanent Restoration delivery i.e. Permanent Restoration delivery until end of study.

The PP analysis set will consist of all subjects fulfilling the inclusion criteria, none of the exclusion criteria and have been treated in accordance with the CIP, e.g. have an implant placed and the final permanent restoration within six months after implant placement, according to Acuris-conometric concept. Treatment efficacy related conclusions will be based on the results from the PP 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.

10.3.1 Primary objective

The primary objective is prosthetic survival 1 year after permanent restoration. The design of the study is a single group study with success/failure reported for the primary variable for each subject. The aim is to estimate the proportion of subjects with “success” (π). The hypotheses of interest are:

$$H_0: \pi \leq \pi_0 \ (\pi_0=90\ \%)$$

$$H_1: \pi > \pi_0 \ (\pi_0=90\ \%)$$

Limit to be tested against is: H_0: 90 %

The null hypothesis will be rejected if the two-sided p-value is less than α (0.025). A p-value

(one-sided) below 2.5 % is considered statistically significant.

The p-value will be calculated using the Binomial test and a two sided exact binomial 95% confidence interval will also be presented.

10.3.2 Secondary objectives

Prosthetic survival 3 and 5 years after permanent restoration.
Analysis equivalent to primary objective will be performed.

Evaluate implant survival rate up to 5 years after permanent restoration.
Proportion of survived implants will be calculated.
A two sided exact binomial 95% confidence interval for the proportion of lost implants will be calculated.

Marginal bone levels alteration up to 5 years after permanent restoration
The measured aspects/sides as well as implants mean value will be presented and used in analysis. Descriptive statistics for absolute values and the change from baseline (Visit 5; Permanent Restoration) will be calculated, in addition the marginal bone level change from implant placement may be calculated. Analysis of the change over time using the Wilcoxon Signed Rank test will be included

Condition of the peri-implant mucosa.
Descriptive statistics will be presented and analysis over time will be included.

Bleeding on Probing (BoP)
Proportion of implants with any bleeding and proportion of bleeding surfaces will be calculated. Analysis of 'any bleeding' over time using the Binomial test will be included.

Plaque
Proportion of implants with any plaque and proportion of surfaces with plaque will be calculated. Analysis of 'any plaque' over time using the Binomial test will be included.

Probing Pocket Depth (PPD)
The measured aspects/sides as well as implant mean value will be presented and used in analysis. Descriptive statistics for absolute values and the change from baseline (Visit 5; Permanent Restoration) will be calculated. Analysis over time using the Wilcoxon Signed Rank test will be included.

10.3.3 Safety analysis

All safety variables will be summarized by means of descriptive statistics. No hypotheses will be tested.

10.4 Determination of sample size

In this study, subjects will receive single crown restorations and the primary objective is prosthetic survival one year after permanent restoration. Studies reporting on implant-supported single crowns found in the literature[17-20], show a prosthetic survival rate of 96.3% (95% CI: 94.2–97.6%) after 5 years. Following this, the expected true prosthetic survival rate, after one year, is set to 97% (=π1).

The aim is to estimate the proportion of subjects with “success”. The hypotheses of interest are

$$H_0: \pi \leq \pi_0 \text{ and } H_1: \pi > \pi_0$$

Limit to be tested against H0: 90 %. The null hypothesis will be rejected if the two-sided p-value is less than $\alpha = 0.025$ and if $\pi = \pi_1$ (97%) the power to reject H_0 should be 90 %.

The formula to calculate the sample size[21] is (n is the number of fully evaluable subjects)

$$n = \left[\frac{\lambda_{\alpha}\sqrt{\pi_0(1-\pi_0)} + \lambda_{1-\beta}\sqrt{\pi_1(1-\pi_1)}}{\pi_0 - \pi_1}\right]^2$$

In the formula λ_x is the x:th quintile of the standardized normal distribution.

As it is a one-sided hypothesis:

α = 2.5 %
λ_{α}= 1.9600
β = 90 % then $\lambda_{1\text{-}0.90}$ 0 1.2816.

Given the assumptions above the sample size is estimated to include 133 evaluable subjects with a power of approximately 90 %.
Assuming a subject drop-out rate of 15 % a total of 157 (=133/0.85) is expected to be included in the study.

10.5 Statistical analysis during the course of the study

Partial clean file will be declared when all subjects have completed:
- Visit 7 (1-year follow-up after PR) – data will be used for 1-year follow-up publication.
- Visit 9 (3-year follow-up after PR) – data will be used for 3-year follow-up publication.

Additional partial clean files may be performed when all subjects have completed:
- Visit 5 (Permanent Restoration) – Demographic and Baseline data

Data base lock will take place and total clean file will be declared when all subjects have completed:
- Visit 11 (5-year follow-up) – data will be used for 5-year follow-up publication.

List of abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CDMS	Clinical Data Management System
CIP	Clinical Investigation Plan
CRF	Case Report Form
DBL	Database Lock
DCF	Data Clarification Form
DD	Device Deficiency
DMP	Data Management Plan
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSI	First Subject In
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions For Use
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
LSI	Last Subject In
LSO	Last Subject Out
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per Protocol
RA	Regulatory Authorities
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SDV	Source Data Verification
USADE	Unanticipated Serious Adverse Device Events
USAE	Unanticipated Serious Adverse Events

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Appendices

Appendix A: CIP signature pages

Signature page - Dentsply Sirona Implants

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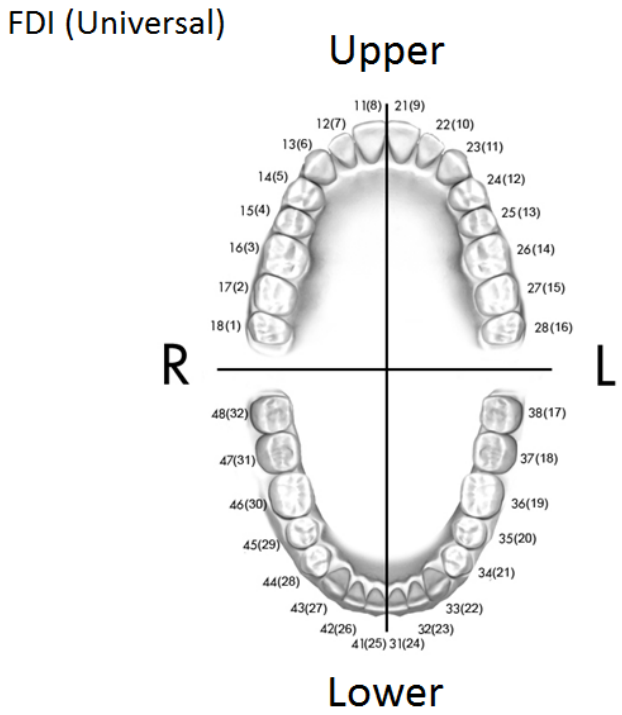
Appendix B: Visit and procedure plan

Visit name	Screening and pre-surgical planning	Implant Placement (IP)	Post-op (PO)	Impression	Permanent Restoration (PR)	Follow-up
Visit number	1	2	3	4	5	6-11
Visit window			IP + 1-2 weeks	IP + max 5 ½ months	IP + max 6 months	PR + 6 months, 1, 2, 3, 4, 5 years (± 1 month)
Written Informed Consent	X					
Inclusion/Exclusion criteria	X	X			X	
Subject demographics	X					
Medical/Surgical history	X					
Oral examination	X					
Radiographic examination	X[1]	X			X	X[3]
Clinical photography[2]	X	X		X	X	X[3]
Implant stability		X		X	X	
Condition of periimplant mucosa (BoP, PPD)					X	X
Plaque						X
Adverse Event documentation		X	X	X	X	X

1 If pre-existing radiographs are insufficient or older than 6 months
2 Clinical photographs will be taken for at least 5 subjects selected by each study site
3 X-rays and clinical photographs will be taken at 1, 3 and 5 year follow-up (visit 7, 9 and 11)

Appendix C: Dental chart

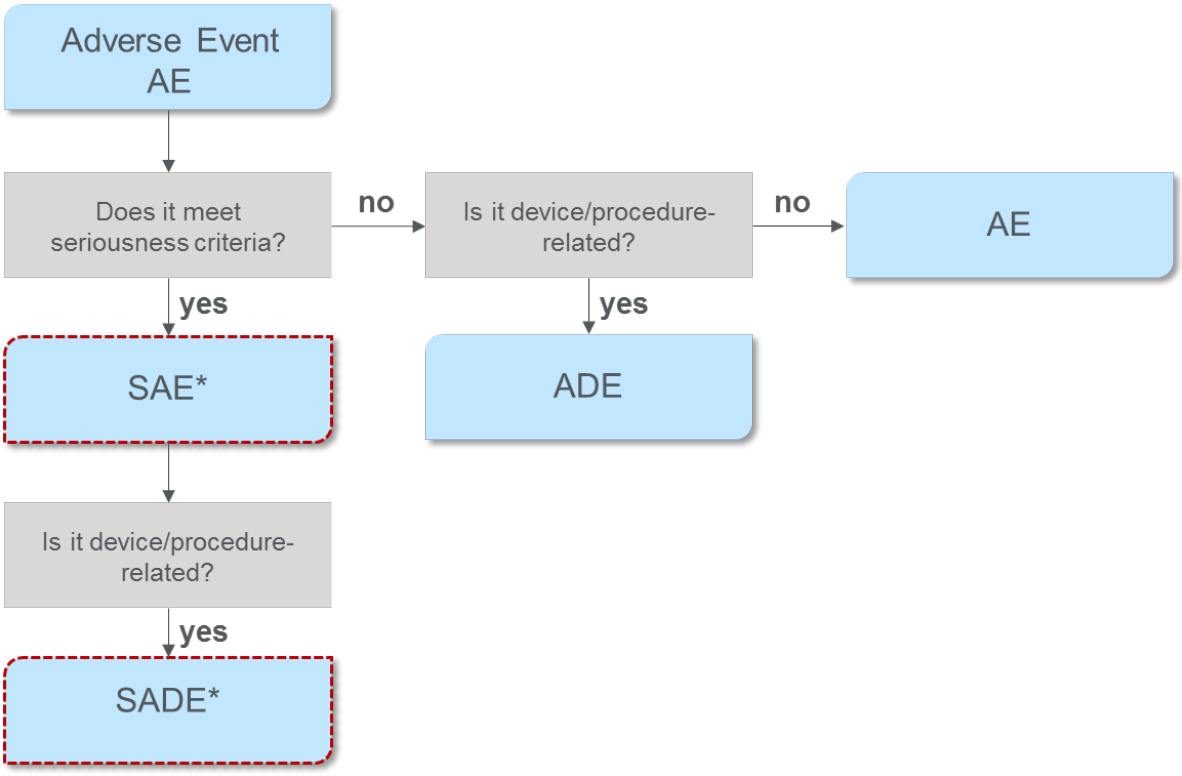
The two-digit-notation system as standardized by the Fédéderation Dentaire Internationale (F.D.I.) is used for the documentation.



Upper				Lower			
Right		Left		Left		Right	
FDI	Universal	FDI	Universal	FDI	Universal	FDI	Universal
11	8	21	9	31	24	41	25
12	7	22	10	32	23	42	26
13	6	23	11	33	22	43	27
14	5	24	12	34	21	44	28
15	4	25	13	35	20	45	29
16	3	26	14	36	19	46	30
17	2	27	15	37	18	47	31
18	1	28	16	38	17	48	32

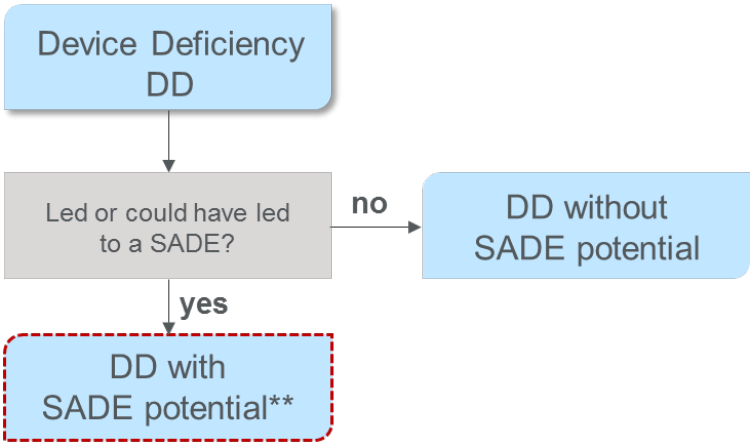
Appendix D: Overview – Types of safety events

Safety events involving subjects:



*SAE and SADE must be promptly reported in the eCRF by the Investigator

Safety events associated with the product itself, not with the subject:



**DD with SADE potential must be promptly reported in the eCRF by the Investigator