CLINICAL INVESTIGATION PLAN

NCT Number	NCT03283241
Study Title:	A randomized, multicentre, double blind, parallel study to evaluate the performance and safety of the Zolidd One ExHex dental implant compared to uncoated One ExHex dental implant in subjects with partial edentulism
Study Code:	ADD-001
Version No:	Version 3.0
Date (YYYY-MM-DD):	2017-07-14

CLINICAL INVESTIGATION PLAN

A randomized, multicentre, double blind, parallel study to evaluate the performance and safety of the Zolidd One ExHex dental implant compared to uncoated One ExHex dental implant in subjects with partial edentulism

Clinical Investigation Plan Code	ADD-001
Clinical Investigation Medical Devices	Zolidd One ExHex and uncoated One ExHex dental implant
Indication	Partial edentulism
Device Class Zolidd One ExHex	Medical device class III combination product
CIP Version	Final Version 3
Date	2017-07-14
Coordinating/Principle Clinical Investigator	Christer Dahlin, Professor, DDS, Käk-kirurgiska Kliniken, Näl Lärketorpsvägen 461 85 Trollhättan Sweden
Sponsor	AddBIO AB Teknikringen 10 583 30 Linköping Sweden

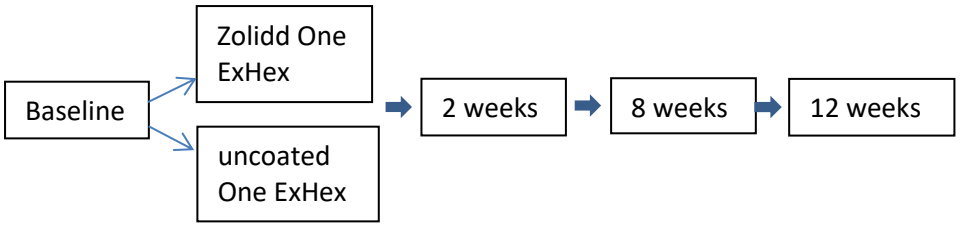
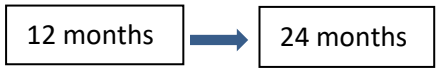
Revision History:

Protocol final version 1 date 2017-02-08	First Protocol
Amendment 1 date 2017-03-10	Amendment after questions from Ethics committee
Protocol final version 2 date 2017-06-14	Minor changes/clarifications including Amendment 1 2017-03-10
Protocol final version 3 date 2017-07-14	Updated after questions from MPA

This clinical investigation will be performed in compliance with ISO 14155:2011, Medical Device Directive (MDD) and the Declaration of Helsinki and applicable regulatory requirements.

1 Clinical investigation synopsis

CIP Number	ADD-001
Version and date	Final Version 3, 2017-07-14
Title	A randomized, multicentre, double blind, parallel study to evaluate the performance and safety of the Zolidd One ExHex dental implant compared to uncoated One ExHex dental implant in subjects with partial edentulism.
Sponsor and manufacturer	AddBIO AB
Investigational Device	Zolidd coated One ExHex and uncoated One ExHex dental implant.
Objectives	Primary Objective The primary objective is to compare the change in stability from day 1 (implantation) to 12 weeks after surgery of the "index implant" between coated and uncoated implants. Secondary Objectives The secondary objectives Part I: • To compare absolute ISQ highest values between coated and uncoated implants for "index implant" at week 8 and week 12 after implantation • To compare safety as assessed by complications post-surgery and any other adverse event up to week 12 between all coated and uncoated implants • To compare change in stability from day 1 to week 8 for the "index implant" for coated and uncoated implants • To compare change in stability day 1 to week 8 and 12 between coated and uncoated implants of all other implants • To compare absolute ISQ highest value at week 8 and 12 between coated and uncoated implants of "index implant" and all other implants • To compare change in marginal bone height between coated and uncoated implants from day 1 to week 8 and 12 The secondary objectives Part II: • To compare safety as assessed by complications post-surgery and other adverse events up to month 24 post-implantation visit between all coated and uncoated implants • To compare survival rate of implants up to 24 months between coated and uncoated implants for the groups and all implants • To compare change in marginal bone height from day 1 to month 12 and 24 between coated and uncoated implants for the groups and all implants . • To compare peri-implantitis frequency at 12 and 24 months between coated and uncoated implants for the groups and all implants,

Overall Investigational design	A randomised, multicentre, double blind, parallel group comparative investigation where subjects will be randomised to receive coated or uncoated implants. The study will consist of two parts (see figure below). Part I, is the main study ending when all subjects have reached visit 5. The study will be evaluated and Clinical Study Report (CSR) will be written for this part. Part II, of the study is a post-follow up study starting when the first subject has completed visit 5. There will be a separate CSR written for Study Part II. The study Part I will begin with a baseline visit, visit 1, Informed consent procedure will take place. Provided the subject will give informed consent for both Study Part I and Study Part II the screening procedure starts. Subjects will undergo all screening and baseline assessment procedures including assessments of dental status to determine number of implants needed. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be given a date for implant surgery within three weeks. The required number of implants will be ordered from the Study Distributor. At the implantation day, visit 2, eligibility will be re-checked before the surgery procedures starts. The subjects who still are eligible will enter the treatment and the implantation surgery is conducted. The first follow-up visit after implantation will take place week 2 post-surgery and the last follow-up visit in Study Part 1 will be at week 12. Any post-surgical complications and adverse events will be collected and recorded in the eCRF. On demand, depending on the outcome of the surgery, additional visits might occur. Study Part II, the Post Follow-up Study, consist of two visits, one at month 12 and another visit at month 24 post-surgery. Post-surgical complications and adverse events from Study Part 1 will be followed-up if not resolved previously. Safety, survival rate and marginal bone loss will be assessed and outcome recorded in the eCRF. Additional visits might occur depending on the status of the subjects. **Part I**  Visit 1 Visit 2 (surgery) Visit 3 Visit 4 Visit 5 **Part II (post follow-up)**  Visit 6 Visit 7

Number of subjects	Seventy subjects will be enrolled to have 62 subjects implanted
Eligibility criteria	Inclusion Criteria: • Male or female subjects aged ≥18 years • Subjects should be willing to take part, able to understand the information given to them, and give written consent • Subject diagnosed with partial edentulism and who needs at least one dental implant in the posterior upper jaw i.e. premolars to first molar. The same subject may also need implants in the posterior mandible (premolars to first molar region)
	Exclusion criteria: • Suspected to be immunocompromised or are taking immunosuppressant • Current participation in another clinical investigation or participation within the last 6 months • Known sensitivity/allergies to any of the test materials or any of their ingredients, such as bisphosphonate, titanium or human fibrinogen • Significant current or past medical history of hepatic, renal, cardiac, pulmonary, digestive, haematological, neurological, or psychiatric disease, hypercalcaemia, previous or ongoing malignancy in the head and neck region or uncontrolled diabetes type I which in the opinion of the Investigator, would compromise the safety of the subject or affect the outcome of the investigation • Pregnant and lactating females or those actively seeking to become pregnant in the next 3 months • Previous (last 5 years) or on-going Bisphosphonate or Denosumab treatment • Significant marginal bone loss prior to implant insertion requiring bone grafting or bone graft substitute • Subject with extraction(s) performed in the position of implant placement within the last 2 months • Subject with need of >6 implants or a full bridge • The final prosthetic construction in need of support from neighbouring teeth • Known drug or alcohol abuse • Subject only need implant(s) in the posterior mandible region
Performance and Safety Endpoints	The primary efficacy endpoint: The primary endpoint is change in stability from day 1 to 12 weeks after implantation of the “index implant” comparing coated and uncoated implants. This will be assessed in terms of induced micro motion of the implant using the Osstell device. The ISQ values are recorded from two directions. The directions should be bucco-lingual and mesio-distal, whereof highest value of the two measurements will be used. The secondary efficacy endpoints Part I: • Absolute ISQ highest value at week 8 and week 12 after implantation for “index implant” • Incidence of post-surgery complications and adverse events up to week 12 post-implantation visit

	• Change in ISQ highest value from day 1 to 8 weeks for the "index implant" • Change in marginal bone height from day 1 to week 8 and 12 for the "index implant" • Absolute ISQ highest value at week 8 and 12 for all implants • Change in marginal bone height from day 1 to week 8 and 12 for all implants The secondary efficacy endpoints Part II: • Post-surgical complications and other adverse events up to month 24 post-implantation visit for all implants • Survival rate up to 24 months for all implants • Change in marginal bone height from day 1 to month 12 and month 24 for all implants • Occurrence of signs associated with peri-implantitis at month 12 and month 24 for all implants

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3 Investigator statement and signature

I confirm that I have carefully read and understood this CIP and agree to conduct the study accordingly. I am aware of, and will comply with the ethical principles that have their origin in the current version Declaration of Helsinki, Good Clinical Practice and all applicable regulatory requirements in that the rights, safety, privacy and well-being of study subjects are protected. I agree to appropriately direct and assist the staff under my control, who will be involved in the study. The signature below constitutes the approval of this CIP and appendices, and provides the necessary assurances that this study will be conducted according to all stipulations of the CIP.

Clinical Site: NÄL, Trollhättan

Site No: 01

Principal Investigator

Print Name_____ Title_____

_____ _____

Signature Date

3.1 Sponsor representative statement and signatures

The undersigned have read this investigation plan and hereby confirm that, to the best of their knowledge, it accurately describes the investigation to be conducted. The signature below constitutes the approval of this CIP and appendices.

CEO
Ulf Sewerin
AddBIO
Linköping
Sweden

_____ Signature

_____ Date

CTO
Anders Petersson
AddBIO
Linköping
Sweden

_____ Signature

_____ Date

Statistics
Nils-Gunnar Pehrsson
CEO/Senior Biostatistician
Statistiska Konsultgruppen
Göteborg
Sweden

_____ Signature

_____ Date

4 Clinical Investigators and Clinical investigation administrative structure

Study role	Name, title, address, and e-mail	Phone No
Coordinating investigator	Christer Dahlin, Professor, DDS, Käk-kirurgiska Kliniken, Näl Lärketorpsvägen 461 85 Trollhättan Sweden Email: dahlinchrister@hotmail.com	+46 (0) 70 5332557 +46 (0) 522 92166
Other Investigators	A list of other investigators and personnel at site will be filed in the ISF and SMF.	
Sponsor representative	Ulf Sewerin, CEO Email: ulf.sewerin@addbio.se Anders Petersson, CTO Email: anders.petersson@addbio.se AddBIO AB Teknikringen 10 583 30 Linköping Sweden Email: info@addbio.se	+46 (0)708797988 +46 (0) 709 741269 +46 (0) 13 21 00 6
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Biostatistician	Nils-Gunnar Pehrsson Statistiska Konsultgruppen Göteborg Sweden Email: ngp@stat-grp.se	+46 (0) 709 63 36 13
Data Management	Pharma Consulting Group AB (PCG) Kungsängsvägen 19 75323 Uppsala Sweden	+46(0)18 430 3100
Blinding and Distribution to site	Inpac i Lund AB Åldermansgatan 2 227 64 Lund Sweden Email: peter.thulin@inpacpharma.com	+46 (0) 46 280 2800

5 List of abbreviations

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Adverse Device Effect
ASTM	American Society for Testing and Materials,
CA	Competent Authority
CE	Conformité Européenne (conforms to European Product Directives)
CIP	Clinical Investigation Plan
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CBCT	Cone Beam Computed Tomography
DD	Device Deficiency
DMFT	Decayed Missed Filled Teeth
eCRF	electronic Case Report Form
EC	Ethics Committee
EMA	European Medical Agency
IB	Investigator Brochure
IFU	Instruction for Use
ISF	Investigator Study File
ISQ	Implant Stability Quotient
GCP	Good Clinical Practice
ISO	International Standard Organization
ITT	Intention-to-Treat
LOCF	Last Observation Carried Over
MDD	Medical Device Directive
MedDRA	Medical dictionary Drug Regulatory Affairs
NAMSA	Independent laboratory
ONJ	Osteonecrosis of the jaw
PP	Per Protocol
PT	Preferred term
QA	Quality Assurance
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedures
SMF	Study Master File
SMP	Study Monitoring Plan
USADE	Unanticipated Serious Adverse Device Effect

6 Introduction and study rationale

Subjects undergoing dental surgery and treatment for the replacement of damaged, decayed or missing posterior maxillary teeth generally face up to 9 - 12 months from initial removal to full usage of their new dental implants[1-5]. Part of this time is linked to healing of bone and gum after initial removal of the subject's own teeth (3-4 months typically), followed by another 3-6 months period whilst the implant is allowed to integrate with the host bone before the final ceramic tooth can be placed onto its supporting implant[6].

Work is on-going to try and shorten this period of time to improve subject's satisfaction with this treatment option. The use of bone graft substitutes at the time of initial surgery to get better bone healing and restoration of gum height has been investigated [7-10].

The ability to improve and shorten the time to the initial integration of the implant within the jawbone are an obvious target for improvement. It is this element of the treatment that AddBIO seeks to address with the Zolidd One ExHex implant.

The Zolidd One ExHex implant consists of generic model of the well-established Nobel Biocare Brånemark MkIV implant, where the surface has been coated with the Zolidd coating.
The Zolidd coating is a nano coating combination of heated fibrinogen and zoledronic acid which adheres to the surface of the screw thread profiles[11-14]. This coating is intended to enhance the bone integration properties of the dental implant. It will be necessary for the Notified Body to gain extra clearance for the pharmaceutical and blood derivative portions of the combination, from the EMA, before granting final CE Mark approval.

This clinical investigation is designed to obtain the necessary confirmatory data of the safety and performance of the use of Zolidd One ExHex implants in subjects with partial edentulism. Subjects will be randomised to receive either Zolidd One ExHex implants or uncoated One ExHex implants. Any one subject will receive a maximum of 6 implants.

A detailed risk- benefit assessment and potential risks due to the investigational procedures are addressed in chapter 9 of this document and in the IB. In this introductory chapter a summary of the main potential issues are discussed.

Implant stability in terms of induced micro motion will be measured during the study with the ISQ device from Osstell. Several papers have been published which use this technique to demonstrate the degree of fixation of the implant within the bone prior to attachment of the appropriately sized dental cap. The results show excellent sensitivity between loose and fixed implants[15-23]. It could be a minor risk for loosening of integration when performing ISQ measurement as early as 8 and when loading at 12 weeks as discussed in chap 9.

In addition radiographic outcome will be assessed to further evaluate clinical performance. There will be intra-oral radiographs taking at two additional times compared to standard treatment in this study. These extra radiographic evaluations are not assumed to add on any potential risks for the subjects. See chap 9.4 in this document for details.
The biocompatibility of the coating has been evaluated by AddBIO in accordance with the established standards. Previous implantations of Zolidd prototype coated implants in both animals and humans have not showed any signs of biocompatibility related problems[31, 14, 32, 33]. There is

however still a risk that a patient will experience adverse reactions associated with hypersensitivity to the coating components[34, 35].
Patients suspected to be immune-compromised or are under immune-suppressant treatment will be excluded (see exclusion criteria chap 14.3.3).

The patient and the surgeon will be informed that patients with known hypersensitivity to any of the product constituents should not be treated with the Zolidd One ExHex implant.

As discussed above the Zolidd coating consists of a nano-coating combination of heated fibrinogen and zoledronic acid which adheres to the surface of the screw thread profiles. The main safety issue of concern is related to the use of zoledronic acid and this has been thoroughly investigated. There have been pre-clinical and clinical investigations on Zolidd prototype coated implants where no adverse device effects have been identified[13, 14]. It should be noted that safety concerns have been raised in the literature and those concerns are associated with long term high dosage treatment with bisphosphonates, leading to osteonecrosis of the jaw (ONJ) when being used to treat metastatic disease etc. in subjects with contributory dental hygiene cofactors. There has been no incidence, observed to date, for osteonecrosis of the jaw occurring in the human studies conducted where bisphosphonates have been applied as a coating on the implant or by direct local bone application during surgery[13, 14]. Thus, there was no significant hazards identified to suggest that the use of RiaSTAP or Zoledronic Acid at the levels obtained in Zolidd coating that would have detrimental effect upon the safety of the subjects. For more detailed information see chap 9 and the IB.

The risk- benefit ratio of Zolidd One ExHex implant in subjects with partial edentulism is judge to be favourable. The major benefit of the Zolidd One ExHex implant is expected to be a shortening of the time for healing while giving a stable implant in areas were the bone quality is not optimal.

7 Identification and description of investigational device

7.1 Description of the investigational device

The test implant, Zolidd One ExHex, and the control implant One ExHex consist of a generic model of the established Brånemark dental implant. The test implant is coated with Zolidd and the control implant is uncoated. Zolidd is a nano-coating combination of heated fibrinogen and zoledronic acid which adheres to the surface of the thread profiles of the dental implants. This Zolidd coating is aimed to enhance the bone integration properties, by strengthening the bone surrounding the implant. The control implant One ExHex is blasted and cleaned according to the same protocol as the coated implant. The only difference between the control and the coated implants are the addition of Zolidd. More details of the coating, individual constituents and the One ExHex implant manufacturing are included in the IB. Both of the coating ingredients of the Zolidd coating have a long established history of use as pharmaceuticals.

7.2 Manufacturer details

The legal manufacturer of coated Zolidd One ExHex and uncoated One ExHex is AddBIO AB, Teknikringen 10, 583 30 Linköping, Sweden. The screw shaped implants and coating of the implants are manufactured for AddBIO by Elos Medtech Timmersdala AB using specially designed equipment. Final sterilization with gamma irradiation will be conducted by Steris.

7.3 Packaging and identification

The coated implant is placed in a custom-made titanium tube with screw on lids, before packaged in a sterile barrier Tyvek pouch. The tube will avoid any potential migration of polymer molecules from vapours generated in the pouch sealing process as well as from surface contact with the inner pouch. The inner pouch is place in an outer pouch (Natural Poly bag) that will act as a moist barrier. Finally, the outer pouch is placed in a carton capsule where a product label is placed. The product label is design as in the figure below. Labelling will be in compliance with 93/42/EEC and applicable harmonized standards. The text "For Investigational Use Only" will be added. The device will be sterilized using gamma irradiation, in accordance with ISO 11737-1, the sterilization method and the package is being validated to confirm product sterility at one year shelf-life. The boxes will be sent to the distributor, Inpac in Lund AB, who will function as a storage depot for the investigational products. The distributor will also be responsible for blinding the products and adding information to the labels as detailed in the figure below.

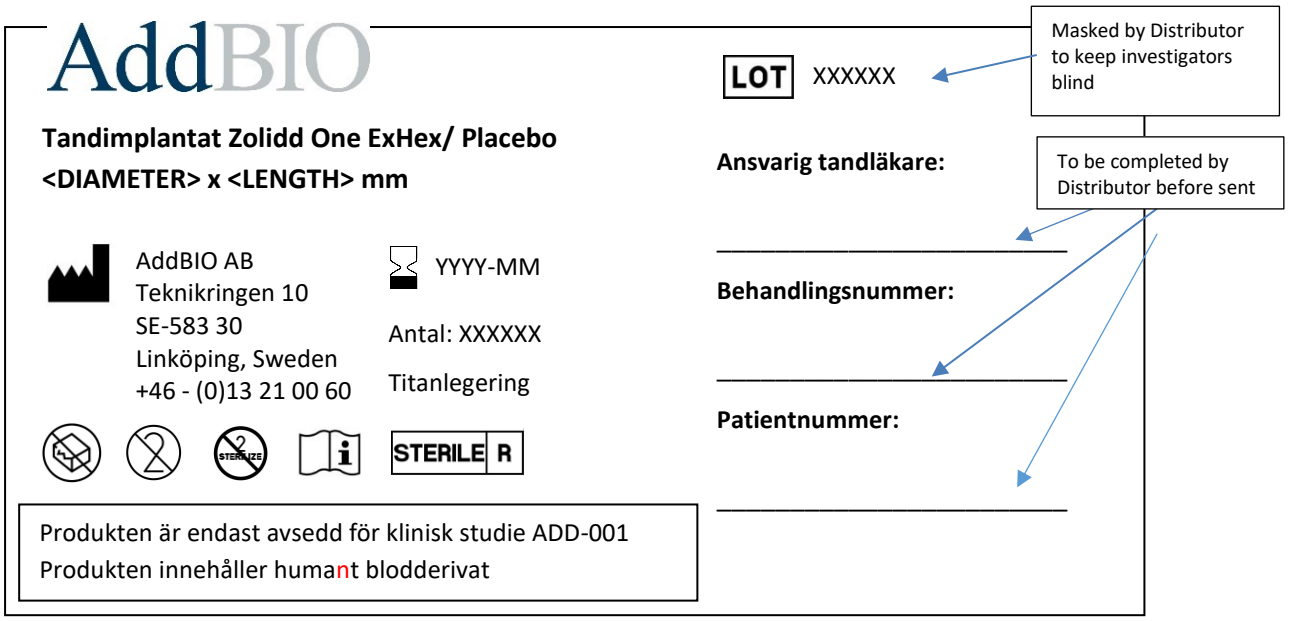


Figure 1 Product label

7.4 Randomization and Ordering of Investigational Products

Once a subject has been enrolled into the study the investigator allocates a study number to the subject selected, in sequential order, from the Site Specific Subject Number List.
The investigator adds this number to the eCRF and contacts the distributor, Inpac in Lund AB, by e-mail as follows:

- order@inpacpharma.com

The investigator informs the distributor, via email, of the subject's study number and number of implants needed for the subject. The distributor acknowledges the order, in return e-mail to the investigator, and provide the date of delivery of the implants.

The distributor will allocate treatment to the subject according to the randomization list provided by Statistiska Konsultgruppen Göteborg, Sweden. This group will also provide treatment code envelopes. The code envelops will be set to each participating site prior to study start. Subjects will be randomly assigned to receive either coated or uncoated implants to a ratio 1:1.

In a controlled way, per allocated randomization number, the distributor will select the number of implants ordered by the investigator and blind the lot number of the implants. Subject's study number, allocated treatment number (same as randomization number) and site details (see Fig 1) will be added to the labels.

Once the Distributor has processed the order the labelled and packaged implants will be sent to the site. Email will be sent to the investigator with shipment details including the tracking number. The investigator will inform the Distributor when the shipment has arrived at site.

7.5 Study Device and Code Envelopes

The investigator will maintain accurate records of all device supplies, including the dates on which device supplies were received from the Distributor (see chap 22).
The identity number of the implant for each randomized subject will be captured in subject's eCRFs. The same information will be documented in the subject's clinical record.

The treatment code envelopes will be kept at the site in a secure place. The location of where the code envelopes are kept must be documented in the subject's clinical record. In case of emergency and at the discretion of the Investigator the code envelope may be opened. If the code is broken this must be documented on the code envelope and in the subject's clinical record. Date and name of the investigator who decided to break the code and the reason will be recorded. At the end of the study the code envelops will be collected and forwarded to the sponsor.

Unused products, still residing with the investigator at the end of study are to be returned to AddBIO for destruction after accountability has been performed.

7.6 Subject populations and indications for use

The sources for recruitment are subjects using the study clinics for their dental care and subjects who are referred to the study clinics from other dental care units. The Zolidd coated One ExHex dental implants are intended to primarily treat subjects requiring replacement of posterior maxillary teeth and as a secondary objective replacement of teeth in the mandibular region. These subjects may suffer from untreatable decay, periodontal disease or an edentulous area. Subject presenting with a maximum of 6 teeth requiring replacement are the target population for the investigation provided they comply with all eligibility criteria and agree to the study procedures.

7.7 Summary of Training and Experience Necessary for Safe Use

All investigators involved in this investigation must be highly experienced in the technique used (Ad Modum Brånemark) and in other current conventional treatments available. At the Site Initiation Visit the investigators and other site staff participating in the study will be trained by a sponsor representative on how to use the device in accordance with the instructions for use (IFU) and the ISQ measurement technique. All protocol procedures, with particular attention to subject eligibility criteria, adverse event reporting, ISO 14155 GCP requirements, informed consent procedures and maintenance of investigator study file (ISF) will be addressed.

The Investigators will maintain records of all site personnel involved in the clinical investigation and complete a delegation list to clarify roles and responsibilities at the study site. The Investigators will ensure that, with the support of the sponsor, appropriate training relevant to the study is given to the site personnel involved in the study and that any new information of relevance for the conduct of the study is forwarded to all personnel involved.

7.8 Description of the use of the device

Full details of the operative technique for the study implants are included in the investigators brochure and the IFU. It is worth noting that the technique used within the study remains the standard technique employed for insertion of similar designed implants as in routine practice.

8 Discussion and Justification of Clinical Investigation Design, Including the Choice of Control Groups

8.1 Clinical Investigation design and choice of control group

The study design (randomized, double blind, parallel groups) was chosen to evaluate the performance and safety of the Zolidd One ExHex dental implant with the uncoated One ExHex implant in subjects with partial edentulism in need of 1-6 implants.

During the baseline visit written informed consent for both Study part I and Study Part II will be collected together with demographics, dental status, medical history and concomitant medications.

At the implantation visit the eligibility criteria will be re-checked to confirm that nothing has changed from baseline to surgery before starting any surgical procedures.

At week 8 and week 12 post-implantation surgery the stability test will be performed using ISQ technique and change in marginal bone height will be measured. Any post-surgical complications and adverse events will be collected and recorded in the eCRF. On demand, depending on the outcome of the surgery, additional visits might occur.

The primary endpoint is stability at 12 weeks after implantation comparing coated and uncoated implant. This will be assessed in terms of induced micro motion of the implant using the Osstell device. The ISQ values are recorded from two directions. The directions should be bucco-lingual and mesio-distal, whereof highest value of the two measurements will be used for the statistical analyses.

8.2 Prior and Concomitant Medication and other Dental Procedures

Medication, which is considered necessary for the subject safety and well-being, may be given at the discretion of the Investigator. At each study visit the Investigator will check for any changes and update the eCRF accordingly.
Investigators will be advised to encourage the subjects to avoid, during the 12 week study period, any dental procedures that could influence study endpoints. Dental procedures needed for the safety of the subjects are excluded from this advice. If a dental procedure is undertaken the clinical investigator must be informed immediately.

9 Risk and benefit analysis

9.1 Anticipated clinical benefits

It is anticipated that the Zolidd One ExHex implant will improve implant stability at 8 and 12 weeks and provide a safer and stronger integration which is a concern especially in compromised bone. Therefore, it is expected that at the time of final prosthetic reconstruction subjects treated with Zolidd One ExHex implants will receive a safer and more predictable stability compared to subjects with uncoated One ExHex implants. This would then present an obvious benefit due to the

improvement in time taken for a subject receiving their final prosthetic reconstruction and a more predictable outcome when the bone quality is poor.

9.2 Anticipated adverse device effects

The most common early post-surgical symptoms in dental implant surgery are swelling, pain, numbness of nerve and/or infection.

Further problems in common include problems associated with failure of the integration or fracture of the implant and/or subsequent loosening, causing revision surgery. These problems may occur but are expected to be of low frequency since the investigational devices used in this study are designed as a generic model of the established Nobel Biocare Brånemark implant with low frequency of such problems.

Known risk factors for long term success are insufficient bone volume, infection, inadequate soft tissue, uncontrolled diabetes, smoking, bruxism, unfavourable jaw relationships, or-facial radiotherapy, and steroid therapy, systemic treatment with bisphosphonates or chemotherapy. The same general precautions apply in this clinical investigation as with any dental implant surgery.

9.3 Residual risks identified in risk analysis report

As part of the risk management process all anticipated risks were reviewed and were either eliminated or reduced to an acceptable level. This process was conducted in line with ISO 14971.

To minimize implant design risks AddBIO has chosen to design the Zolidd One ExHex as a generic model of the established Nobel Biocare Brånemark MkIV implant, used for decades with high success-rates.

In dental implant surgery, the risk of bisphosphonate related osteonecrosis of the jaw (ONJ) is well known. This condition is however related to long-term systemic bisphosphonate treatment. It should be noted that the Zolidd surface, the amount of bisphosphonate, is very low when compared to a systemic injection. It is also known that local treatment with bisphosphonates is less prone to ONJ than systemic treatment [12] and not any of the previous studies performed in animal models exhibited any signs of ONJ[14, 30-32]. There has been no incidence observed for osteonecrosis of the jaw in the two human studies conducted where bisphosphonates have been applied as a coating on the implant or by direct local bone application during surgery[13, 14]. For more information see the IB. For this reason, the risk of causing osteonecrosis of the jaw is deemed as negligible.

The fibrinogen concentrate used in the coating (RiaSTAP®, CSL Behring, Germany) is derived from human blood plasma pools as documented by CSL Behring certificate of analysis. CSL Behring has its own plasma collection centres and an Integrated Safety System in place to ensure that all of its plasma products, including RiaSTAP®, meet the highest possible safety standards. Despite the above standard measures, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. Given the broad use and rigorous quality control of RiaSTAP, it is AddBIOs conclusion that the risk probability is extremely low and that the potential benefit of the Zolidd coating thus outweighs this risk. More information is available in the IB. The patient will be informed about the potential risk of transmission of pathogens through the patient information form.

9.4 Risks associated with participation in the clinical investigation

ISQ measurement is performed at 8 and 12 weeks with the aim to measure the stability of the implants. There is a minimal risk for loosening of integration when testing the integration already at 8 weeks and when loading the implants at 12 weeks. However, if loosening of integration would happen the implant can be either left in-situ for prolonged healing or replaced with a larger diameter implant. Replacement of a failed implant will be made by commercial brand at the discretion of the Investigator.

Standard procedure prior to determining if the subject is a candidate for dental implant treatment will be applied. It involves adequate and individual radiographic evaluations in order to establish bone quality and quantity as well as location of anatomical structures in the area of implantation.

Furthermore, participation in the study involves intra-oral x-ray films on 5 occasions and 1 pre-surgery CBCT scan or alternative radiograph for bone quality and quantity evaluation. Of these 6 radiographic evaluations, two are extra for taking part in this study. Taking worst case scenario where subject has the maximum 6 implants widely spread through-out the mouth this would mean a maximum of 6 images per radiographic assessment, of which would be a maximum of 5 time points (post-implantation 2, 3, 12 & 24 months), and one CBCT pre-surgery.

Each bitewing/intra oral film delivers a dose of 0.5 micro Sieverts, the maximum exposure would be 1x1000 (CBCT) and 6x5x0.5 = 1015 micro Sieverts in 24 months. This compares to the typical background irradiation level in Sweden of 1000 micro Sieverts per year. Thus, it equates to 1015/2000 = 50% compared to background dose over a period of 2 years.

Additional known or expected risk in this clinical study are those that would be expected for normal routine treatment of this condition with currently available treatment alternatives. In addition, there is a risk for allergies or other reactions of the surface treatment with the bisphosphonate and blood protein. These risks are very small as the dose is 1000 times lower of the bisphosphonate and the blood protein used clinically. Subject with known sensitivity/allergies to the test material or any ingredients are excluded from participation, see exclusion criteria.

9.5 Possible interactions with concomitant medical treatments

Currently there is no indication to suspect any potential interactions between Zolidd coated One ExHex implants and routine existing subject concomitant medications.

9.6 Steps to be taken to control or mitigate risks

The Zolidd One ExHex dental implant has been reviewed as part of the risk management process in accordance with ISO 14971:2012, for all stages of the product's lifecycle. The risk management will be updated throughout the development process until all risks have been mitigated as far as can be reasonably expected and where the benefits of the device can be deemed to outweigh the residual risks.

9.7 Risk-Benefit conclusion

The major benefit of the Zolidd One ExHex implant is expected to be a shortening of the time for healing while giving a stable implant in areas were the bone quality is not optimal. Risks have been mitigated as far as possible and the risk-benefit ratio of using Zolidd One ExHex for partial edentulous subjects participating in this investigation is judged to be favourable (benefit is higher than risk).

10 Objectives and hypotheses for the clinical investigation

The objective of this investigation is to evaluate the efficacy and safety of Zolidd One ExHex implants when used for the intended purpose. Primary evaluation will be week 12 after implantation at end of Study Part I. Data will continue to be collected at month 12 and 24 for a second analysis at 24 months after implantation as part of the Post Follow-up of the device Part II.

Where a subject receives more than one implant, the most posterior maxillary implant will be considered to be the "index implant", which will be assessed for performance as primary objective. In a case where the subject also has mandibular implants more posterior than the most posterior maxillary implant the maxillary implant will still be considered to be the "index implant".
In a case where subject have bilateral teeth in same location the investigator will be free to select one of these teeth to be the "index implant", but will document his reasoning for selection before implantation and shall be recorded in eCRF.
All implants will be followed regardin safety and performance (efficacy) however the "index implant" will as primary be comparing coated and uncoated devices

10.1 Primary objective

The primary objective is to compare the change in stability from day 1 (implantation) to 12 weeks after surgery of the "index implant" between coated and uncoated implants.

10.2 Secondary Objectives

The secondary objectives Part I:

- To compare absolute ISQ highest values between coated and uncoated implants for "index implant" at week 8 and week 12 after implantation
- To compare safety as assessed by complications post-surgery and any other adverse event up to week 12 between all coated and uncoated implants
- To compare change in stability from day 1 to week 8 for the "index implant" for coated and uncoated implants
- To compare change in stability day 1 to week 8 and 12 between coated and uncoated implants of all other implants
- To compare absolute ISQ highest value at week 8 and 12 between coated and uncoated implants of "index implant" and all other implants
- To compare change in marginal bone height between coated and uncoated implants from day 1 to week 8 and 12

The secondary objectives Part II:

- To compare safety as assessed by complications post-surgery and other adverse events up to month 24 post-implantation visit between all coated and uncoated implants
- To compare survival rate up to 24 months between all coated and uncoated implants for the groups and all implants
- To compare change in marginal bone height from day 1 to month 12 and 24 between all coated and uncoated implant for the groups and all implants
- To compare frequency of peri-implantitis between coated and uncoated implant for the groups and all implants

10.3 Hypotheses

It is anticipated that there will be improved early change in stability observed with the coated compared to the uncoated implants, determined with change in ISQ highest values from day 1 to 12 weeks after insertion. See Statistics section for further details.

11 Design of the clinical investigation

This is a randomised, multicentre double-blind, parallel study where subjects will be randomised to receive coated or uncoated dental implant screws. Subjects will be assessed during the 12 weeks' post-operative period with an extended Post follow-up period up to 24 months after implantation.

11.1 Primary and secondary endpoints

11.1.1 Primary efficacy endpoint

The primary endpoint is change in stability from day 1 to 12 weeks after implantation of the "index implant" comparing coated and uncoated implants. This will be assessed in terms of induced micro motion of the implant using the Osstell device. The ISQ values are recorded from two directions. The directions should be bucco-lingual and mesio-distal, whereof highest value of the two measurements will be used.

11.1.2 Secondary efficacy endpoints for Part I:

- Absolute ISQ highest value at week 8 and week 12 after implantation for "index implant"
- Incidence of post-surgery complications and adverse events up to week 12 post-implantation visit
- Change in ISQ highest value from day 1 to 8 weeks for the "index implant"
- Change in marginal bone height from day 1 to week 8 and 12 for the "index implant"
- Absolute ISQ highest value at week 8 and 12 for all implants
- Change in marginal bone height from day 1 to week 8 and 12 for all implants

11.1.3 The secondary efficacy endpoints Part II are:

- Post-surgical complications and other adverse events up to month 24 post-implantation visit
- Survival rate up to 24 months for all implants
- Change in marginal bone height from day 1 to month 12 and month 24 for all implants
- Occurrence of signs and symptoms with peri-implantitis at month 12 and month 24 for all implants

12 Investigational device treatment

12.1 Description of the device technique to be used

The dental implants used in this study are of a typical generic design but without the CE mark. The devices are produced by Elos Medtech Timmersdala AB, Sweden. A single size 4 diameter by 10mm long external hex screw implant will be used in the study. The devices are manufactured in medical grade pure titanium and comply with relevant ISO and ASTM Standards for dental implants.

The implants will be placed using standard technique for one-stage procedure. The implants will have a healing abutment placed at first surgery but the implants will not be loaded directly with the prosthetic reconstruction. An instruction for the use of the surgical procedure is detailed in the IFU. Further detailed instructions for the use are given in the Investigator Brochure.

12.2 Description of investigational devices

12.2.1 Investigational Device – Zolidd One ExHex Dental Implant

AddBIO is the legal manufacturer of the Zolidd coated One ExHex dental implant screw.

12.2.2 Comparator Device One ExHex

Same design as the investigational device but uncoated dental implant screw.

12.3 Description of equipment used for assessment during investigation

Bitewings should be taken in the same direction and place each time. Therefore, creating and using a stent is preferable. No calibration of Osstell is needed, always chose the higher of the two values from each reading, without taking notice to direction.

13 Study schedule, visits, procedures and assessments

Subject enrolment will take approximately 9-12 months to complete. Each subject has a 12 week follow-up post-surgery for Part I and an additional 24 month for Part II.

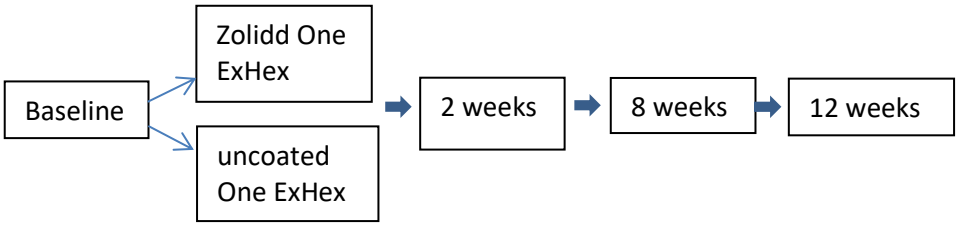
The study will consist of two parts (see figure below). Part I is the main study ending when all subjects have reached visit 5. The study will be evaluated and a Clinical Study Report (CSR) will be written for this part. The total time from baseline to visit 5 will be approximately 14 weeks.
Part II of the study is a post-follow up study starting when the first subject has completed visit 5. The other subjects are included, on an ongoing basis, as they have completed visit 5. There will be a separate CSR written for Study Part II.

The study Part I will begin with a baseline visit, visit 1, Informed consent procedure will take place. Provided the subject will give informed consent for both Study Part I and Study Part II the screening procedure starts. Subjects will undergo all screening and baseline assessment procedures including assessments of dental status to determine number of implants needed. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be given a date for implant surgery within three weeks. The required number of implants will be ordered from the Study Distributor.

At the implantation day, visit 2, eligibility will be re-checked before the surgery procedure starts. The subjects who still are eligible will enter the treatment and the implantation surgery is conducted. The first follow-up visit after implantation will take place week 2 post-surgery and the last follow-up visit in Study Part 1 will be at week 12. Any post-surgical complications and adverse events will be collected and recorded in the eCRF. On demand, depending on the outcome of the surgery, additional visits might occur.

Study Part II, the Post Follow-up Study, consist of two visits, one at month 12 and another visit at month 24 post-surgery. Post-surgical complications and adverse events from Study Part I will be followed-up if not resolved previously. Safety, survival rate and marginal bone loss will be assessed and outcome recorded in the eCRF. Additional visits might occur depending on the status of the subjects.

Part I



Visit 1 Visit 2 (surgery) Visit 3 Visit 4 Visit 5

Part II (post follow-up)

Visit 6 Visit 7

13.1 Study visits and Schedule of events

13.1.1 Baseline, visit 1

Subjects will be asked to participate in the investigation and read and sign Informed Consent Form (ICF). After all questions has been answered and that the consent has been signed subject will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria. If the subject meets all criteria they will be scheduled for surgery within 3 weeks with exception for subjects undergoing extraction of teeth. Investigator will schedule surgery as appropriate for these patients.

The following information will be collected and recorded:

- Demographics
- Medical history
- Concomitant medications
- Pregnancy test (urine dip stick, fertile woman)
- Dental Status
  - General oral examination to evaluate status of s status of soft tissues and pre-operative radiographic evaluation to assess bone quality[1] and alveolar ridge height and confirm suitability for implantation.
  - Decayed Missed Filled Teeth (DMTF).
  - Details of existing fillings, periodontal status, extractions and caries requiring further dental intervention.
  - All teeth to be replaced as part of the treatment for this investigation will be selected and the ‘“index implant”’ i.e. the most posterior maxillary site will be identified for the primary evaluation, all other implants will be followed for secondary evaluation.

13.1.2 Surgery, visit 2

Details of surgical technique performed at implantation of implants included, any deviation from the standard protocol must be documented in the eCRF together with the reason for deviation.

The following information will be collected during surgery:

- Change in dental status
- Information about number of implants and locations
- General surgery information
- X-ray to assess bone height
- Any adverse events and/or adverse device effects will be collected and reported in the right section in the eCRF
- Any change in concomitant medication

13.1.3 Week two post-surgery, visit 3

Subject will return to clinic at week 2 post-surgery for follow-up and removal of stitches if placed

The following information will be collected:

- Post-operative complications and Adverse events
- Any contacts/visits at site since surgery before this visit 3

13.1.4 Week eight post-surgery, visit 4

Subject will return to clinic at week 8 post-surgery for follow-up.

The following information will be collected:

- General oral examination and ISQ evaluation for all implants ” will be evaluated.
- X-ray evaluation to assess bone height
- Post-operative complications and Adverse events
- Any changes of concomitant medication
- Any contacts/visits at site since surgery before this visit 4

The primary focus will be the ‘“index implant”’ but all implants will be evaluated. Details of any other dental interventions or significant changes in concurrent conditions and/ or medications will also be documented.

13.1.5 Week twelve post-surgery, visit 5

Subject will return to the clinic at week 12 post-surgery for Part 1 final assessments and start of the Prosthetic phase.

The following information will be collected:

- Change in dental status
- General oral examination and ISQ evaluation for all implants will be evaluated.
- X-ray evaluation to assess bone height
- Post-operative complications and Adverse event
- Any changes of concomitant medication
- Any contacts/visits at site since before this visit 5

The prosthetic device should be placed; including information on the type (single crowns or a bridge) will be recorded in the eCRF. This visit will end the Part 1 of the study and an analysis will take place. A new appointment will be scheduled for the Post-follow up Study at month 12.

13.1.6 Post follow-up 12 month, visit 6, Study Part II

Subjects will be asked to return to the clinic at 12 months' post-surgery for follow-up of the implants(s). The primary focus will remain the '"index implant"' but all implants will be evaluated

The following information will be collected:

- General oral examination for all implants, , will be evaluated.
- X-ray evaluation to assess bone height
- Survival rate of implants
- Major dental interventions
- Complications and Adverse event
- Any changes of concomitant medication

13.1.7 Post follow-up month 24 visit 7

Subjects will be asked to return to the clinic at 24 months' post -surgery for follow-up of the implants(s). The primary focus will remain the '"index implant"' but all implants will be evaluated

The following information will be collected:

- General oral examination for all implants, , will be evaluated.
- X-ray evaluation to assess bone height
- Survival rate of implants
- Major dental interventions
- Complications and Adverse event
- Any changes of concomitant medication

Table 1 Schedule of events; Study Part I and Study Part II

		Study Part I				Study Part II	
Visit Number	1	2	3	4	5	6	7
Day/month	Baseline -60 to - 1 days	Day 1 Surgery	2 weeks	8 weeks	12 weeks	12 month	24 month
Assessment/event							
Informed consent	X						
Inclusion/exclusion criteria	X	X[1]					
Demographics	X						
Medical History	X						
Concomitant medication	X	X		X	X	X	X
Oral examination[2]	X	X		X	X	X	X
Pre-surgery radiographics[3]	X						
X-ray[4]		X		X	X	X	X
ISQ[5]		X		X	X		
Surgery		X					
Stitches removed			X				
Adverse event		X	X	X	X	X	X
End of Part 1[6]					X		
End of Part II[6]							X

[1] Re-confirm inclusion and exclusion criteria
[2] Soft tissue and dental status and changes from previous visit
[3] Bone quality, ridge height and suitability for implantation and/or signs of loosening
[4] Marginal bone height and signs of loosening of integration
[5] ISQ examinations, higher value must be recorded
[6,] if a subject discontinues before end of Part 1 (visit 4) and/or end of Part II (visit 6) a termination page must be filled in with the reason for the premature discontinuation

14 Study population

Approximately 70 subjects will be screened to ensure 62 subjects to be enrolled, 31 subjects in each study group. The study is planned to be conducted in 4 sites in Sweden. A complete list of participating sites will be filed in the ISF and SMF.

14.1 Enrolment of subjects

Subjects seeking or being referred to the selected clinics for treatment of edentulous area in the posterior region of the mouth, with at least one tooth to be replaced in the maxillary region, will be asked to participate in the clinical investigation.

14.2 Informed consent procedures

Informed consent must be obtained prior to the subject entering into the study and before any study related procedures are performed. In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s) and adhere to the current versions of ISO 14155 GCP standard and the Declaration of Helsinki. The potential subject should be provided with a written and oral explanation of the study. It is the Investigators responsibility to

ensure that each study subject is fully informed about the nature of the study, its purpose, expected duration, procedures, the benefits and risks involved. Each study subject should also be informed of their right to withdraw from the study at any time without prejudice.

The informed consent must be obtained by a medically qualified Investigator. Another site staff can assist in informing the subject. Subjects should be given ample time to ask questions to the Investigator. To properly document the informed consent process, the Investigator should record notes in the subject's medical record, and both the Investigator who conducted the informed consent procedure and subject are required to sign and date the informed consent form.

A copy of the signed and dated informed consent form should be given to the subject and the original form should be filed in the ISF.

14.3 Subject screening and Subject identification logs

Investigators must keep a record of all subjects who were considered for enrolment even if they were not subsequently found suitable for the investigation. This information is necessary to verify that the subject population was selected without bias. A screening log will be provided for the purpose.

Subjects eligible for the treatment phase will be allocated a code number in connection with enrolment. Investigators must keep a confidential ID list with the latest known address and contacts of all subjects enrolled into the study linking the code number to each subject´s full identity.

14.3.1 Subjects inclusion procedures

The 70 subjects planned to be screened and the 62 subjects to be enrolled in this study will be carefully evaluated that they meet all inclusion criteria and none of the exclusion criteria; this will be recorded in the eCRF and in the Subject's clinical record.

14.3.2 Inclusion criteria

The subject is eligible for inclusion in the study if all of the following criteria are met:

- Male or female subjects aged ≥18 years
- Subjects should be willing to take part, able to understand the information given to them, and give written consent
- Subject diagnosed with partial edentulism and who needs at least one dental implant in the posterior upper jaw i.e. premolars to first molar The same subject may also need implants in the posterior mandible (premolar to first molar region)

14.3.3 Exclusion criteria

The subject is not eligible for inclusion in the study if any of the following criteria are met:

- Suspected to be immunocompromised or are taking immunosuppressant
- Current participation in another clinical investigation or participation within the last 6 months
- Known sensitivity/allergies to any of the test materials or any of their ingredients, such as bisphosphonate, titanium or human fibrinogen
- Significant current or past medical history of hepatic, renal, cardiac, pulmonary, digestive, haematological, neurological, or psychiatric disease, hypercalcaemia, previous or ongoing malignancy in the head and neck region or uncontrolled diabetes type I which in the opinion of the Investigator, would compromise the safety of the subject or affect the outcome of the investigation
- Pregnant and lactating females or those actively seeking to become pregnant in the next 3 months
- Previous (last 5 years) or ongoing Bisphosphonate or Denosumab treatment

- Significant marginal bone loss prior to implant insertion requiring bone grafting or bone graft substitute
- Subject with extraction(s) performed in the position of implant placement within the last 2 months
- Subject with need of >6 implants or a full bridge
- The final prosthetic construction in need of support from neighbouring teeth.
- Known drug or alcohol abuse
- Subject only need implant(s) in the posterior mandible region

14.4 Prohibited concomitant therapy

Extensive dental treatment during the study period which may interfere with the outcome of the investigated device is not allowed. If a subject need any of the follow interventions the monitor must be contacted.
The following is not permitted:

- Connecting the prosthetic reconstruction to neighbouring teeth.

14.5 Premature termination

Subjects will be made aware of their right to terminate involvement in this investigation at any time and for whatever reasons without affecting their right to further treatment and to an appropriate follow-up investigation.
Subjects who are diagnosed and need to start treatment for osteoporosis will be excluded from the study prematurely.
The reason for any withdrawal must be documented in the appropriate eCRF page. If a subject is withdrawn from the study, the Sponsor must be notified immediately.

14.6 Termination or suspension of the study

In the event that the investigation generates an excessive frequency of unanticipated adverse device events a premature termination or suspension of the study will be considered. Premature termination or suspension may be requested by the competent authority, ethics committee or the Sponsor at any time.

In the event a study site does not comply with regulations, lack of recruitment or poor quality data the site will be prematurely closed.

Any decisions to terminate or suspend the investigation early or to close a study site will be notified in writing to both to the Investigators, Regulatory authority and the relevant Ethics Committees.

The Sponsor retains the right to terminate the investigation for non-safety reasons by giving an appropriate period of notice to all involved parties as per contractual agreements in the Clinical Study Agreement (CSA).

15 Adverse Events/Adverse Device Effect, Serious Adverse Event/Serious Adverse Event Effect and Device Deficiencies

15.1 Definition of Adverse events (AE)

Adverse Events are defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal laboratory finding), in subjects, users or other persons whether or not considered related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational device or the comparator.

NOTE 2: This definition includes related to the procedure involved.
NOTE 3: For users or other persons, this definition is restricted to events related to Investigational medical device

15.1.1 Adverse device effects (ADE)

Adverse event related to the use of an investigational medical device.

Note 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instruction for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
Note 2 This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

15.1.2 Serious adverse events (SAE)

Adverse Event that:

a. Leads to a death, injury or permanent impairment to a body structure or body function
b. Leads to a serious deterioration in the health of the subject, that either resulted in:
    1. a life-threatening illness or injury or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalisation or prolonged hospitalisation,
    4. in medical or surgical intervention to prevent life-threatening illness
c. Leads to foetal distress, foetal death or a congenital abnormality or birth defect

15.1.3 Pregnancy

If women become pregnant during the study she must be excluded from further study related examinations and follow-up visits.
The investigator should report all pregnancies within 24 hours of awareness to the sponsor.
The pregnant subject will be followed until the end of the pregnancy. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death or other serious infant condition must be reported and followed up as an SAE.

15.1.4 Serious adverse device effects (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

15.1.5 Unanticipated Serious adverse device effects (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report.

15.1.6 Device deficiencies (DD)

Inadequacy of an investigational medical device related to its identity, quality, quality, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

15.1.7 Reporting of Adverse Events/Adverse Device Effects

All subjects will be carefully monitored for the occurrence of AEs during the investigation period from the run-in to the completion of follow up. The Clinical Investigator will collect AE information using non-leading questions such as "have you experienced any new health problems or worsening of existing conditions". Events directly observed or spontaneously volunteered by subjects will also be recorded.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the subject or reported in response to an open question by the Clinical Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information.

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding the medical device
- Opinion on causality
- Seriousness
- Outcome

Severity will be assessed using the following definitions:

Mild	Aware of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.

The relationship to investigational device will be assessed by the Investigator using the following definitions:

Not related	Evidence exists that the adverse event definitely has a cause other than the investigational device (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
Unlikely	The relationship with use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related	A temporal relationship exists between the event onset and use of investigational device. Although the adverse event may appear unlikely to be related to the investigational device, it cannot be ruled out with certainty; and or the event cannot be readily explained by the subjects' clinical state or concomitant therapies.
Probably related	A temporal relationship exists between the event onset and administration of investigational device, and appears with some degree of certainty to be related based on known mechanism of action of the device. It cannot be readily explained by the subjects' clinical state or concomitant therapies.

Causal relationship (Definitely related)	Strong evidence exists that the investigational device caused the adverse event. There is a temporal relationship between the event onset and administration of the investigational device including user error. There is strong mechanistic evidence that the event was caused by the investigational device. The subject's clinical state and concomitant therapies have been ruled out as a cause.

Any AE's that are possibly, probably or definitely related will be classified as ADE.

15.2 Reportable events and Emergency contact details

All serious events:

- Any SAE
-
- Any Device Deficiency(DD) that might have led to a SAE if (a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate
- New finding/updates in relation to already reported events

that occur during the investigation, including death, ***must be reported to the sponsor or it's representative immediately (within one working day***) ***but no later than 3 calendar days*** after investigators awareness of the event
The reporting will be performed electronically via the eCRF (Viedoc ™). The site staff will log into Viedoc ™ and enter all available information regarding the reportable even in the AE Log for the specific subject. As soon as the event is saved as "serious" in Viedoc ™, an email alert will immediately be sent to the medical Monitor and AddBIO.
In case any additional documentation should be required, PCG will request this information from the study site. All reportable events must be followed until resolution or until the investigator assesses them as being under full control. .
In case the eCRF is out of order, or no internet access is available at the study site, the reportable event should be reported using a paper copy form, which will be available at the site and should be completed manually. The completed, signed and dated report should, within 24 hours, be faxed to:

PCG Clinical Services AB
Att: PCG Pharmacovigilance
Fax number: +46 (0) 18 4444 823

The study site should notify the local CRA via phone or email about the submission of the SAE report. As soon as the personnel have access to Viedoc ™, the SAE should be reported electronically as well

Sponsor will follow the procedures for reportable events to the Competent Authority as outlined in MEDDEV 2.7/3 revsion 3 May 2015 and must report to Competent Authority immediately, but no later than 2 calendar days after awareness for any event that is death, serious injury, or serious illness and that requires remedial action for subject, users or other person.
Any other new finding/update, immediately, but no later than 7 calendar days following the date of awareness of the sponsor.

15.2.1 Emergency contact sponsor

Irene Herrmann, DDS, PhD Consultant Södra Småskolevägen 41 429 44 Särö	 +46 (0) 708 93 66 13 Email: ireneeherrmann@hotmail.com

16 Monitoring

The Sponsor is responsible for selecting qualified clinical sites in this clinical investigation and to ensure the proper conduct of the clinical study at each site respectively. The sponsor's personnel or authorized designee will monitor all clinical sites in a manner consistent with ISO 14155 GCP standard, applicable SOPs, health authority regulations and the clinical research standards adopted by the sponsor (legal manufacturer). Monitoring will be done at Interim Monitoring Visits throughout the study and a Site Closeout Visit.

The Site Selection Visit will be performed to document that the site can perform the study according to the protocol. When EC and CA approval has been obtained a Site Initiation Visit will be planned to train all involved study staff.
During the study Interim Monitoring Visits will be performed to ensure protocol compliance and data collection.
Site Close-out Visit will be performed when all data has been collected and all queries have been resolved (after database lock).

The monitor will at the visits and between the visits:

- Provide information and ongoing support to the Investigator
- Verify that facilities remain acceptable
- Verify that the investigational team is adhering to the CIP, ISO 14155 GCP standard and applicable regulations
- Verify completeness, accuracy and consistency of the data collected
- Conduct source data verification, which will require direct access to all original records for each subject (e.g. medical records)

The monitor will maintain a close contact with the study site between monitoring visits through letters, e-mail or telephone calls to clarify any issues and to ensure the study is being carried out according to plan and the CIP.

Site management and monitoring are further specified in the Study Monitoring Plan (SMP) issued for this study.

All documentation and correspondence pertaining to the investigation (source data, letters etc.) should be kept in accordance with ISO 14155 GCP standard. The monitor will issue reports from all visits that will be reviewed by AddBIO or designate. In these reports problems will be identified, and resolution by corrective action will be tracked and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing the eCRFs are resolved.

All formal monitoring visits and/or other communication between Sponsor, Monitor, Investigator, or any other regulatory body (Ethics, CA) will be documented in specified format as per sponsor procedures and kept in accordance with ISO 14155 GCP Standard.

Full details regarding site monitoring will be covered in a separate Site Monitoring Plan (SMP) document.

16.1 Subject Records and Source Data

Data may be recorded directly in the eCRF, which will then be considered as source data. This must be documented in the SMP before the study starts.
The origin of source data in the investigation will be further specified in SMP ("Origin of Source Data").
It is the responsibility of the Clinical Investigator to record essential information in the medical records in accordance with national regulations and requirements, including:

- Investigation code
- Subject screening number and/or subject number
- That informed consent for participating in the study was obtained
- Diagnosis
- All visits during the investigation period
- All AEs/ADEs
- All SAE/SADEs
- All DD
- Treatments and medications
- The identification of the device
- Location of Code envelopes

The Clinical Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Signed sections of eCRFs will be monitored and collected on a regular basis.

16.2 Access to Source Data and Documentation

The Clinical Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the EC, if required.

17 Quality assurance

AddBIO is responsible for independent quality assurance (QA) audits of the clinical investigation processes, if deemed needed. Audit of the investigation sites may be conducted to assess and help assure the compliance with ISO 14155 GCP Standard and applicable regulatory requirements. The sites may be subject to a QA audit by the Sponsor or its representatives, as well as inspected by Competent Authorities (CA) and Ethical Committees (EC). This implies that auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the investigation and must have access to source documents, including subjects' medical records. By participating and signing this CIP this the Investigator agrees to this requirement.

18 Statistical considerations

18.1 Statistical and analytical plans

The principal features of the statistical analysis of the data are described in this section. A more technical and detailed elaboration of the principal features will be written in a separate statistical analysis plan (SAP) and is to be finalised prior to database lock Part I. When the investigation up to week 12 is completed and the data are assembled, a blinded review of the planned analysis in Part I at the clean file meeting will be carried out. The review will concern the definition of outliers, violators, and exclusion of subjects or data from the analysis sets. Decisions made in connection with

the review will be documented. The SAP will be reviewed and could be updated as a result of the review of the data. The database lock to Part I will contain only study variables measured up to and include visit week12. Tables, figures and CSR to Part I will be based on this first database lock.

When study Part II is completed and the data are assembled, a new blinded review for Part II will be carried out at this second clean file meeting. The second database lock will be performed for Part II based on data after 12 weeks visit. The final CSR will be based on all locked data.

18.2 General methodology

The design of the study is a two parallel group design. The main efficacy analyses will be performed on the Intention-to-Treat (ITT) populations between the two groups. Complementary performance analyses will be performed on the Per Protocol (PP) population. See section 18.4 below.

For comparison between the two randomized groups regarding “index implant”, Fisher’s non-parametric permutation test will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, and Chi-square test for non-ordered categorical variables and Fisher’s exact test for dichotomous variables.
For primary efficacy variables and for other important continuous efficacy variables the 95% confidence interval for the mean difference between the two groups will be obtained by inversion of Fisher’s non-parametric permutation test by means of simulation.

For comparison between the two randomized groups regarding analysis of all teeth within subjects a mixed model with random effects analysis adjusting for within subject correlation will be used.

If significant clinical relevant differences are found between the two randomised groups in important baseline variables, then complementary efficacy analyses will be performed adjusted for these variables.

For comparison over time within randomized groups Fisher’s non-parametric permutation test for paired observations will be used for change in continuous and Sign test for change in ordered categorical variables or change in dichotomous variables.

The distribution of the variables will be given as mean, SD, median, minimum and maximum for continuous variables and as number and percentages for categorical variables.

Time to loss of implant will be described with Kaplan-Meier curves and analysed with Log-rank test between the two randomised groups.

All significance tests will be two-sided and conducted at the 5% significance level.

18.3 Statistical hypothesis

Primary Objective – the hypothesis is that there will be improved early stability of the ‘“index implant”’ observed with the coated than with the uncoated implants, determined with change in ISQ values from day 1 to 12 weeks after insertion.

Secondary Objectives – the hypothesis is that there will be improved early stability of the “index implant”” observed with the coated than with the uncoated implants, determined with change in ISQ values from day 1 to 8 weeks after insertion.

Furthermore– the hypothesis is that there will be improved early stability of all implants observed with the coated than with the uncoated implants, determined with change in ISQ values from day 1 to week 8 and 12 after insertion and determined with ISQ values at week 8 and week 12.
The hypothesis is also that there will be less marginal bone loss for coated compared to uncoated implants from implantation to week 8 and 12.
At the post follow-up visits at month 12 and 24 it is anticipated that this difference will be greater in the maxillary teeth as mandibular bone is usually of better quality. At month 12 and 24 post follow-up compare safety, survival rate and change in marginal bone height from implantation between coated and uncoated implants.

18.4 Analyses Datasets (statistical populations)

18.4.1 Intention to treat (ITT) population

The ITT population will include all randomized subjects with at least one performance measurement after implantation. The final definition will be made at the clean-file meeting for Part I before the breaking the code.

18.4.2 Per protocol (PP) population

The Per Protocol population will include all subjects in the ITT-population without significant protocol violations. Subjects identified as protocol violators will be documented and agreed on at the clean-file meeting for Part I before the database lock for Part I.

18.4.3 Safety population

Safety population will include all subjects who have received at least one implant.

18.5 Performance Analyses

18.5.1 Primary efficacy analysis

Primary efficacy analysis will be the comparison of change in ISQ highest value for coated implant with change in ISQ highest value for the uncoated implant on the “index implant” from day 1 to 12 weeks visit with Fisher’s non-parametric permutation test on the ITT-population at significance level 0.05. For primary efficacy variable the 95% confidence interval for the mean difference between the coated and the uncoated implants is obtained by inversion of Fisher’s non-parametric permutation test by means of simulation.
If the 12 months ISQ highest values are missing Last observation carry forward (LOCF) will be used from 8 weeks.
If significant differences are found between the two randomised groups in important baseline predictors a complementary primary efficacy analyses will be performed adjusted for these variables using analysis of covariance (ANCOVA).

Sensitivity analyses will be performed for primary efficacy variable change in ISQ highest value from day 1 to week 12 between coated and uncoated implants with multiple imputations for missing values using analysis of variance for the unadjusted analysis and analyses of covariance for the adjusted analysis if needed. When using multiple imputations LOCF should not be applied.
Complementary analyses between the two randomized groups of the primary efficacy variable will be done on the PP-population.
Primary efficacy analysis will be presented per centre and a separate analysis will also be performed in order to study centre effect for primary variables. In case of few centres, centre will be analysed as fixed effect.

18.5.2 Secondary efficacy analyses Part I

Secondary performance analyses for Part I will be the comparison will be the comparison between the two randomized groups regarding all the secondary performance variables given in section 11.1.2 using the statistical methodology given in sections 18.2 above on the ITT-population. Complementary analyses between the two randomized groups of secondary performance variables will be done on the PP-population.

18.5.3 Secondary efficacy analyses Part II

Secondary performance analyses for part II will be the comparison will be the comparison between the two randomized groups regarding all the secondary performance variables given in section 11.1.3 using the statistical methodology given in sections 18.2 above on the ITT-population. Complementary analyses between the two randomized groups of secondary performance variables will be done on the PP-population.

18.5.4 Exploratory performance analyses

Univariable and multivariable analyses of baseline predictors to primary and selected secondary outcome variables will be performed using linear and/or logistic univariable regression analyses followed by forward stepwise multivariable linear and/or logistic regression analyses.

18.6 Safety analysis

Adverse events (AE) will be listed and summarised by body system, incidence, severity, seriousness and duration/outcome. All AE's will be coded with MedDRA dictionary and tabulated by Preferred Term (PT) code and System Organ Class (SOC) code. Serious Adverse Events (SAEs) or Serious Adverse Device Effects (SADEs) will be summarised separately. Any premature discontinuations due to adverse events and deaths will be listed and summarised by treatment group.

Time to loss of implant will be described with Kaplan-Meier curves and analysed with Log-rank test between the two randomised groups.

All safety analyses will be performed on the safety population.

18.7 Analysis of baseline variables

All baseline variables will be tabulated by randomised group and analysed by randomised group according to the statistical methods given in the statistical methods given in section 18.2 above on both the ITT population and PP population.

18.8 Determination of sample size

The power analysis based on Abtahi et al. 2012: The SD for change in ISQ value from placement to month 6 was 5.3 in the active group and 5.4 in the control group. In order to be able to find a clinical difference of five ISQ highest values in change between placement and 12 weeks between the coated and the uncoated group with Fisher's non-parametric permutation test with 90% power 28 evaluable subjects are needed in each group assuming a SD for change in ISQ in each group of 5.6 and a significance level 0.05. Thirty-one subjects will be randomized to each study group to compensate for 10% drop-out. A total of 62 subjects will be randomized to the two groups.

18.9 Randomisation procedure

Subjects will be randomised in proportions 1:1 to receive either coated or uncoated screw implants. This will be in a balanced block design; the sequences and sizes of blocks may also be randomised. The aim being to maintain a balance in subject numbers across all centres in the investigation at any one time, provided recruitment rates are similar.

Once generated the central randomisation schedule will be kept blinded for the study monitor, investigators and data management staff. After un-blinding for analyses of Part I the study monitor and investigator should still be blinded regarding study patients.

Coated implants batches will be kept separate from uncoated batches and suitably labelled to allow easy identification prior to final packaging before sterilisation. Placement in final packaging and labelling with standard labels including Subject ID Number will be supervised and double checked. Further details of this process are included in the Investigator brochure as is the procedure for emergency code breaking.

18.10 Expected drop-out rates

It is anticipated that the dropout rate for this investigation should be low and based on previous work a dropout rate of less than 5% would be expected. The above figures include sufficient subjects to cover this margin.

18.11 Interim analysis

No interim analysis is planned.

18.12 Reporting deviations from original statistics plan

Deviation from original statistical plan will be specified in the statistical Analysis Plan (SAP).

18.13 Sub-group analysis plans

Interaction analyses will be performed between baseline variables and group effect, coated vs uncoated, regarding primary efficacy variable.
Interactions effect with ($p<0.10$) will be followed by suitable subgroups analyses for that baseline variable.

18.14 Handling missing or spurious data

Last observation carry forward (LOCF) will be used from 8 weeks to 12 weeks in Part I and from 12 months to 24 months in Part II. For primary efficacy analyses a sensitivity analysis will be performed with multiple imputations.

18.15 Subject distribution in multicentre studies

It is planned to include 3-4 clinics recruiting each approximately 5-20 subjects.

19 Data management

19.1 The web-based e-CRF

Clinical data (including AEs and concomitant medications) will be entered into an eCRF (Viedoc™) provided by PCG. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. The data path – from data entry via the web interface over internet to storage in the database, and browsing over Internet - is fully validated by system design, testing and data validation. All the processes – development, testing, configuration, user training, staff training, support, and operation and disaster recovery – are fully validated in compliance with 21 CFR Part 11, ISO 14155, the Helsinki declaration and local medical and data protection acts. Authorised trial site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorised trial site personnel prior to the trial being initiated and any data being entered into the system for any trial patient.

AddBIO will not have exclusive control of the trial data reported in the eCRF at any time. All data generated in the clinical trial relevant to the patients will be made under the control of the Investigator at all times during and after the trial. PCG will therefore ensure that a contemporaneous certified copy of the data will be created before PCG transfer the data to AddBIO and this certified copy must be retained at the Investigator site. The Investigator should be informed about the process.

19.2 Data, database validation, query resolution, security and access

All data will be reported in the eCRFs and/or diary cards either directly or from other Source Documents such as subject notes etc. At each site a Source Document Identification List must be completed by the responsible Investigator, prior to study start, to identify the location of source data and consequently enable the monitor to do a proper check of the eCRF entries against the source documents. The monitor should be fully aware of all source documents available at the site and verify site staff follows set procedures.

eCRF's will be reviewed during monitoring visits for data accuracy and completeness and where appropriate any outstanding data queries raised and resolved. eCRF data will be compared to source documents to ensure there are no discrepancies. All entries, corrections and alterations are to be made by the Investigator or designee in the e-CRF.

Confidentiality of all data, especially subject sensitive data will be guaranteed through contractual obligations and professional standards of work practices by the clinical affairs and data management staff involved in this project. Subjects will be allocated a study number which will be entered on the eCRF. Only coded data will be transferred to the sponsor. Access to this data will be limited to those directly involved in the project and where data is stored it will be in a limited access environment both physically and electronically stored data being held securely and encrypted as appropriate.

19.3 Data retention

In line with the requirements of local regulations, the MDD 93/42/EEC and ISO 14155 the legal manufacturer will effectively retain the data from this investigation for 15 years after the lifetime of the device on the market.

Investigators are obligated to retain the data as long as required by the local applicable regulation which usually is for 10 years after final signed CSR. Data include any original source documents related to the study, including the Subject Identification List, the original signed informed consent forms and detailed records of medical device use. AddBIO should be contacted before any study related documentation is planned for destruction. The data can be held at a third party secure location if required.

19.4 Data QA procedures

This study will be conducted in compliance with ISO 14155 GCP standard and any other local laws and/or regulations. AddBIO CLINSOPs apply unless other SOPs held by selected CRO are agreed. When other SOPs will be used they will be detailed in the contract with the selected CRO and AddBIO.

20 Amendments to the clinical investigation plan

Investigator may not amend the protocol without prior written permission of the Sponsor. If the CIP needs to be amended, the amendment must be agreed by both the sponsor and the investigators and approved by regulatory authority and by the ethics committee before implementation. Approval must also be obtained for updates to the written informed consent, when applicable.

An exception to above is a change of CIP procedures to eliminate immediate hazards to the study subject.

21 Clinical investigation plan deviations

Every effort should be made to comply with the requirements of the protocol. Prior approval by the Sponsor is required for changes in or deviations from the CIP, except in an emergency. If the changes or deviations may affect the rights, safety, or welfare of participants, IRB/IEC approval is required. Deviations will be recorded with an explanation for the change. The Sponsor is responsible for analysing the deviations and assessing their significance. Corrective action will be implemented to avoid repeat deviations.

Repeated and serious failures in Investigators or subject compliance will need to be addressed severely as they have the potential to affect both subject safety and investigation outcome. Refer to Section 14.6.

22 Device accountability procedures and storage

Accurate device accountability is an important and key element of the Sponsor's ability and obligation to be able to trace all investigational devices used in a clinical investigation. AddBIO will ensure records are kept to document the location of all investigational devices from shipment to site until return and destruction. The site will be supplied with Accountability Logs which must be continuously updated by the site staff.
The Investigator is responsible for ensuring the accountability logs received from the sponsor are accurately maintained. The logs must accurately reflect the accountability of the device product at all time. The site monitor will review these during monitoring visits.
All investigational products should be stored in an appropriate securely locked room with limited access at the trial sites.
All material supplied is for use only in this clinical investigation and should not be used for any other purpose. At the end of the investigation, the remaining investigational devices will be returned to the sponsor after the conclusion of the study.

23 Statement of compliance

23.1 Relevant ethical and regulatory standards and guidelines

The investigation will be conducted under the terms of the current versions of Declaration of Helsinki, and ISO 14155 Clinical investigation of medical devices for human subjects -- Good clinical practice. The investigation will also follow the requirements of the appropriate annexes of MDD 93/42/EEC.

Regulatory authority and Ethics Committee approval must be in place prior to start the study.

23.2 Clinical indemnity insurance provision

The Sponsor will maintain insurance coverage for the duration of the investigation as required by applicable local regulations. All relevant documentation regarding such insurance will be filed in the Study Master File and at each site as appropriate (ISF).

24 Publication policy

Once the study is approved and before the initiation the investigation will be notified to one of the appropriate clinical investigation databases in compliance with Declaration of Helsinki and publication policies.

After completion of the study, a Clinical Investigation Report will be prepared and reported according to ISO 14155 GCP standard. Key results will be made publicly accessible.

Publication policy will follow Declaration of Helsinki. Negative and inconclusive as well as positive results will be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest will be declared in the publication.

Prior to submitting for publication, presenting, using for instructional purposes, or otherwise disclosing the results of the investigation, the investigator agrees to allow AddBIO a period of at least 30 days (or, for abstracts, at least 10 working days) to review the proposed publication or disclosure prior to its submission for publication or other disclosure.

For this multicentre study, the first publication or disclosure shall be a complete, joint multicentre publication or disclosure. This statement does not give AddBIO any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of AddBIO proprietary confidential information.

25 List of references

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26 APPENDICES

26.1 Appendix I Declaration of Helsinki

World Medical Association - Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in

the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship

with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best

proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

26.2 Appendix 2 Instructions for Use

AddBIO

Instructions for use Zolidd One ExHex – SE
Date: Revision 4 2017-04-28

AddBIO AB, Teknikringen 10
SE-583 30, Linköping

Produktbeskrivning

Zolidd One ExHex är ett dentalimplantat som tillhandahålls i två olika utföranden, dels obelagda och dels belagda med den bioaktiva beläggningen Zolidd.

De belagda implantaten har belagts med ytan Zolidd för att påskynda inläkningen av implantatet, speciellt i områden med sämre benkvalitet. Zolidd består av ett nanolager humant blodprotein samt bisfosfonat.

Implantatet är ett skruvformat titanimplantat (titan grad 4) av storlek Ø4.0x10mm med en marginalanpassning för R (reguljär 3,75 och 4mm) profil så kallad ”external hex design”.

Implantatet är en generisk variation på Nobel Biocares originalimplantat designat av MkIV och därav kompatibelt med kirurgiska och protetiska komponenter för MkIV.

Kompatibilitet

Implantatet är kompatibelt med instrument, borr och protetiska komponenter från Nobel Biocare, enligt *ad modum* Brånemark.

Indikationer

Partiellt tandlöshet

Varningar, försiktighetsåtgärder och kontraindikationer

Samma generella försiktighetsåtgärder gäller som vid alla dentala implantatoperationer.

Endast käkkirurger eller tandläkare med lång erfarenhet av att installera dentala implantat i enlighet med *ad modum* Brånemark skall använda AddBIOs implantat.

Kända riskfaktorer inkluderar otillräcklig benvolym, infektion, otillräcklig mjukvävnad, okontrollerad diabetes, rökning, bruxism, ogynnsamma käkförhållanden, oro-facial strålbehandling, steroidbehandling, systemisk behandling med bisfosfonat samt cellgiftsbehandling.

Patienter med allergier mot titan, zoledronat (bisfosfonat) eller andra bisfosfonater, eller fibrinogen-koncentrat bör inte behandlas med detta implantat.

Fibrinogen framställs från blod som kommer från bloddonatorer. Vid tillverkningen vidtas speciella åtgärder för att förhindra att infektioner överförs till patienter. Detta inkluderar ett noggrant urval av blod- och plasmagivare för att säkerställa att personer med risk för att vara smittbärare utesluts, samt test av enskilda donationer och plasmapooler för tecken på virus/infektion. Tillverkaren av läkemedlet inkluderar dessutom steg i hanteringen som kan inaktivera eller avskilja eventuella virus. Trots detta kan risken för överföring av infektion inte helt uteslutas när läkemedel framställda ur humant blod eller plasma ges. Detta gäller även okända eller nya virus och andra typer av infektioner.

Implantatet är säkert vid MR undersökning men kan orsaka bildartefakter.

Sterilitet

Implantaten tillhandahålls sterila. Om antingen implantatet eller förpackningen verkar skadade, om utgångsdatum passerat eller om steriliteten av något annat skäl ifrågasätts, ska implantatet inte användas. Produkten får inte återanvändas eller om-steriliseras då detta kan påverka ytbeläggningen negativt.

Tillvägagångssätt

1. Patienten förbereds för implantatoperation med en utvidgad medicinsk och oral undersökning.

2. Benkvalitet och viktiga anatomiska strukturer fastställs med hjälp av lämpliga röntgenologiska utvärderingar i de tandlösa posteriora områdena.

3. Vid operationstillfället skall området bedövas, vanligtvis med lokal bedövning.

4. Tandköttet klaffas upp enligt implantatkirurgisk standardmodell.

5. De fastställda implantatsätena (kan vara enstaka eller multipla) markeras med ett rundborr eller direkt med spiralborr. Därefter borras de med spiralborr med stigande storlek från Ø2.0x10mm till ”Twist step drill” Ø2.4/2.8 x10mm och ” Ø2.8/3.2 x10mm för de mjukaste kvaliteterna. När benet ger mer motstånd som i medium till hårt ben kan även ett Ø3.2/3.6 x10mm borr användas. Följ instruktionerna enligt IFU för MkIV. Max borrhastighet är 2000 varv/minut med adekvat NaCl spolning.

Borrdjupet blir ca 1mm djupare än angiven markering på borret p.g.a. borrets spets, varför det krävs > 2mm distans till närliggande anatomiska strukturer.

6. Implantatsätet förgängas ej, och implantatet installeras med maxhastighet 25 varv/minut och med max 45 Ncm. När implantatet nått sitt rätta läge i sätet skall kirurgen manuellt känna att det är stabilt. ISQ skall användas för att mäta stabiliteten.

7. En läkdistans sätts på implantatet och operationssåret sys ihop.

8. Eventuella stygn tas bort efter ca 2 veckor

9. Implantationen sker enligt så kallad 1-stegsförfarande. Det vill säga att en läkdistans placeras på implantatet vid operationstillfället. Direkt belastning av implantatet skall undvikas under inläkningsperioden på 3 månader.

10. Inför avtryckstagning avlägsnas först läkdistansen. Sedan skall ISQ mätas för att fastställa att stabiliteten är acceptabel. Har stabiliteten minskat i stället för ökat jämfört med det tidigare ISQ värdet bör förlängd inläkningstid övervägas. Är implantatet helt mobilt kan ett nytt implantat sättas i sätet. Avtryck för protetik sker efter att läkdistansen avlägsnats och enligt gängse förfarande med avtryckstagning med öppen sked först. Läkdistansen sätts tillbaka på plats igen till dess att det protetiska arbetet är klart och skall sättas på plats.

11. Implantatavtrycket tillsammans med ett avtryck på motstående käke och en bitning skickas till tandtekniskt lab. för framställning av lämplig protetisk konstruktion.

12. När protetiken är klar tas läkdistansen av och protetiken ansluts. Den protetiska (bro)konstruktionen skall passa passivt utan att någon kraft används när den skruvretineras på plats enlig *ad modum* Brånemark.

13. Post-protetisk uppföljning sker enlig standardförfarande *ad modum* Brånemark med årlig oral undersökning och röntgen efter år 1 och 2 därefter med längre intervall.

14. Patienten informeras om hur man håller rent kring sina ersättningar och om att utan dröjsmål kontakta behandlande tandläkare vid eventuella besvär.