Within patient comparison of immediately loaded and non-loaded submerged and transgingival healed implants within 4 months

A controlled clinical pilot study

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Sponsor's study protocol code:

Comparison of loaded and non-loaded implants

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2. List of abbreviations

FPFV	**First Patient First Visit**
LPLV	**Last Patient Last Visit**
BASG	**Federal Agency for Safety in Healthcare**
IIS	**Investigator Initiated Studies**
CE	**Conformité Européene**
PTV	**Periotest Values**
3D	**Three Dimensional**
OHIP	**Oral Health Impact Profile**
MPG	**Medical Devices Act**
90/385/EEC	**European Directive on implantable medical devices**
KALG	**Styrian Hospital Act**
KAKuG	**Federal Law on hospitals**
ENISO	**European Norm**
ISQ	**Implant stability Quatient**

3. Responsibilities and addresses

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4. Synopsis

Sponsor	**Univ.-Prof. Dr.med.univ. Walther Wegscheider**
Name	Within patient comparison of immediately loaded versus non-loaded submerged and transgingival healed implants in the edentulous mandible
Running head	Comparison of loaded and non-loaded implants
Target population (or indication)	Age 20-80 Men and women Edentulous Mandible
Study design	Controlled Clinical Trial
Aims of the clinical trial	Primary aim of the trial Marginal bone loss in different implant healing protocols over the first 4 months Secondary aims of the trial Implant survival rate Measurements of Periotest / ISQ values Biologic and prosthetic complications Patients satisfaction
Outcome measures (endpoints) of the clinical trial	Primary outcome measure periimplant bone level change in mm Secondary outcome measures Implant survival rate Measurements of Periotest / ISQ values Biologic and prosthetic complications Patients satisfaction
Number of patients	20
Time schedule	With reference to the trial Recruitment period: December 2016 Planned start (FPFV):February 2017 Planned end (LPLV):December 2018 With reference to patients Duration of treatment: 4 months
Inclusion criteria	• *Written consent of the participant after being informed*

	• *Capability of giving an informed consent* • *good health as defined by the subjects medical history (no contraindications as described in the exclusion criteria below)* • *age 20 to 80 years* • Patients who require 6 implants in the positions 32, 33, 34, 42, 43, 44 • *edentulous mandible with enough interforaminal bone volume for placement of 6 implants* • Residual vertical bone height of at least 8mm in the interforaminal region • Patients who wish implant-supported restoration with six implants
Exclusion criteria	• *Homelessness* • *Smoking* • *Medication with a contraindication for implant therapy* • *Skeletal immaturity* • *Any active malignancy or ongoing treatment for malignancy* • *An active infection at the operative site* • *Persistent compartment syndrome or neurovascular residua of compartment syndrome* • *Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone* • *Contraindications to the class of devices under study, e.g. known hypersensitivity or allergy to class of devices* • *Pregnancy* • *Intention to become pregnant during the course of the study* • *Breast feeding* • *Lack of safe contraception*
Medical device:	Commercial name: AstraTech Implantsystem AstraTech Scanbodies Cerec Omnicam Simplant Software Manufacturer: Dentsply Implants / Dentsply Sirona
Treatment plan	Implantat placement of AstraTech implants using surgical guide in the interforaminal region located at positions 34, 33, 32, 42, 43, 44. First intraoperative Surface Scan with Cerec Omnicam (Sirona) and Astratech

	Scan Bodies (Dentsply Implants). Intraoperative impressions (Polyether impression material) Manufacturing dolder bar on 33, 43 and immediately loading the implants by integration into existing mandibular dentures 32, 42 transgingival healing using AstraTech healing abutments (Dentsply Implants) 34, 44 covered and left to heal Second Stage surgery and Surface Scan after 3-4 months. Full thickness flap. Recovery of the remaining implants after healing period of 3-4 months and scan of the periimplant marginal bone level. Analysis with Simplant Software (Dentsply Sirona) to evaluate the periimplant marginal bone loss. Additionally comparison of bone loss for each patient measured by probing and on right-angle intra-oral radiographs taken at the time of implant placement and 3-4 months postoperative. Measurements of Periotest / ISQ values Evaluation of OHIP-G 14 Oral Health Impact Profile

5. Scientific background

This document is a protocol for a clinical human research study. This study is to be conducted according to international standards of Good Clinical Practice and the current version of the Declaration of Helsinki (ICH-GCP Guidelines).

A successful prosthetic therapy with dental implants relies on adequate bone quality and quantity to ensure long term stability (Brugnami et al. 2009).

According to the Brånemark protocol a stress-free healing period is one of the most emphasized requirements for implant integration (Adell et al. 1981). Therefore implant placement is traditionally a two-stage procedure. Traditionally, after the implant placement the implants are covered by soft tissue and left to rest during a healing period to minimize loading forces, contamination with bacteria and relative movement (Becker et al. 1997). 4-6 months after implant placement, in which the process of osseointegration has started, a second surgical procedure is necessary to expose the implants for further prosthetic treatment. Besides non-loaded submerged implants, which require a two-stage surgery, the non-loaded implants may also heal transgingival using a healing abutment.

Several clinical studies suggest a progressive shortening of this healing period. In addition, immediate loading has been proposed for the edentulous mandible to shorten dental rehabilitation time (Ericsson et al. 2000; Becker et al. 1997; Chiapasco et al. 1997; Tarnow et al. 1997).

Immediate implant loading is defined as implant placement with primary stability and prosthetic loading with provisional prosthetic teeth at the same time. The purpose of this study is to compare reproducible parameters of immediately loaded and non-loaded submerged and transgingival healed osseointegrated implants by the change in bone levels. The outcome measurements are based on clinical stability and on changes of marginal bone level between implant placement and 4 months later (healing period of non-loaded implants).

In a preliminary prospective study at the Department of Dentistry and Maxillofacial Surgery Graz the clinical outcomes of 14 immediately loaded implants were compared to 28 non-loaded implants (7 patients, each 6 implants in the edentulous mandible). (Lorenzoni et al. 2003)

Each of these patients obtained 6 implants in the interforaminal region of the lower jaw located at positions 34, 33, 32, 42, 43, 44. The upper edges of these implants were placed at the bone level and the necessary primary stabilities of 45 Ncm were achieved. The bone level in relation to the implant margin was measured with a 1-mm gauge periodontal prove and estimated to the nearest 0.5mm. Four of the six implants were covered with cover screws.

To obtain a within patient comparison of immediately loaded and non-loaded implants, the ones at position 33 and 43 were chosen to be immediately loaded by a Dolder-bar retained overdenture. These implants were connected with a transfer coping and impressions were made with polyether. Within a period of 2-4 days of manufacturing, a Dolder-bar was integrated on these two implants.

After a delayed healing period of 6 months, second stage surgery was carried out. At this time, a full thickness flap was raised, exposing the margin of all involved implants in order to collect as much information as possible about clinical differences between loaded and non-loaded implants. The clinical parameters to be evaluated at this point were: survival rate, measurement of Periotest values (PTV, (Schulte & Lukas 1993) after mounting the gingiva formers, and assessment of marginal bone level related to the bone level at first stage surgery for loaded and non-loaded implants. Periodontal probes of 1-mm calibration were utilized for the assessment of the distance between the coronal bone level and the upper edge of the implant.

Six months post-op, the median of bone level changes was 1mm reduction of periimplant bone height for the loaded implants and 0.5mm reduction for the non-loaded implants. The corresponding mean values were 0.9mm (∫0.40) and 0.33mm (∫0.34), respectively. The control of significance level was achieved the same way as for the Periotest values. With P_0.001, this difference was highly significant (Lorenzoni et al. 2003).

In our present study we want to confirm the outcomes of the former study by acquiring more precise data about the marginal bone remodelling using surface scans. In addition the bone remodelling differences between submerged and transgingival healed implants should be analysed.

Based on the results of the present pilot study, we intend to conduct a subsequent trial with two groups (immediately loaded vs. delayed loaded implants).

6. Name and description of investigational devices

All implants, cover screws and healing abutments used in this study will be from ASTRA TECH® Implant System EV (Dentsply Implants, manufacturer: DENTSPLY IH GmbH, Steinzeugstraße 50, 68229 Mannheim, Germany). The implants are *Osseospeed EV S* and *Osseospeed EV C* with the corresponding cover screws. The implants have different diameters and lengths (diameter 3.0-4.8 mm / length 8.0-13.0mm). The healing abutments are *Healing Uni EV* with the corresponding diameters (3.0-4.8mm) and different heights (3.0 or 4.0 mm). Each implant, cover screw, and healing abutment has an article number as well as a traceable number for direct identification. The implants, cover screws and healing abutments are used for common placements of dental implants and the healing procedures afterwards.

The scanbodies used in this study will be from Sirona Dental Systems GmbH (Fabrikstraße 31, 64625 Bensheim, Germany) and are named *Scanbodies für Omnicam*. The scanbodies have an article number as well as a traceable number for direct identification. The scanbodies are used for a common impression procedure, where a digital impression of the mandible will be taken (after implant placement and second-stage surgery).

The intra-oral camera for the digital impression will be *CEREC Omnicam AC* (manufacturer: Sirona Dental Systems GmbH (Fabrikstraße 31, 64625 Bensheim, Germany). The intra-oral camera has an article number as well as a traceable number for direct identification. The intra-oral camera is used for a common impression procedure, where a digital impression of the mandible will be taken (after implant placement and second-stage surgery).

The Impression material for the conventional impressions will be *AquasilUltra* (manufacturer: Dentsply DeTrey GmbH (De-Trey-Straße 1, 78467 Konstanz, Germany). The impression material has an article number as well as a traceable number for direct identification. The impression material is used for a conventional impression procedure, after implant placement for manufacturing the Dolder bars for immediate loading.

The used software for transmitting and evaluating the data taken by the intra-oral scanner will be *Simplant Software* from Dentsply Implants (manufacturer:

DENTSPLY IH GmbH, Steinzeugstraße 50, 68229 Mannheim, Germany) in its current version.

The implant stability will be evaluated using the Periotest M - measurement device (manufacturer: Medizintechnik Gulden e.K., Eschenweg 3, 64397 Modautal, Germany) and Ostell IDx ISQ measurement device (manufacturer: Osstell AB, Stampgatan 14, 411 01 Göteborg, Sweden)

All used investigational devices are CE-certified.

The indications for which these investigational devices are used are: good health as defined by the subjects medical history (no contraindications as described in the exclusion criteria below), age 20 to 80 years, edentulous mandible with enough interforaminal bone volume for placement of 6 implants.

The training and experience required for the implant placement and the treatment afterwards are: licensed dentist. Anyway, all surgical procedures will be performed by an experienced clinician.

The implant-storage is located at the Department of Dentistry, Oral and Maxillofacial Surgery Graz. The investigators maintain accurate records of the components used in specific patients. All the parts used will be registered and documented for each patient.

7. Rationale for the structure of the clinical trial

The comparison of different healing protocols has already been performed using different measuring methods. In a former study performed at the Medical Universtiy Graz it has been shown that the Periotest values of loaded implants were significantly higher compared with those of non-loaded implants, but still in the normal range of well osseointegrated implants.

Six months post-op, the median of bone level changes was 1.0 mm reduction of periimplant bone height for the loaded implants and 0.5 mm reduction for the non-loaded implants (Lorenzoni et al. 2003).

Based on this former study we performed a sample size estimation. A sample size of 8 in each group will have 80% power to detect a difference in means of -0,580 (the difference between a Group 1 mean, μ_1, of -0.910 and a Group 2 mean, μ_2, of -0.330) assuming that the common standard deviation is 0.380 using a two group t-test with a 0.05 two-sided significance level. When the sample size in each of the 3 groups is 9, a one-way analysis of variance will have 80% power to detect at the 0.05 level a difference in means characterized by a Variance of means of 0.060, assuming that the common standard deviation is 0,380.

Based on these statistical calculations and considerations on possible dropouts, a patient sample size of 20 was determined.

To measure the bone remodelling for different healing protocols of dental implants (transgingival, submerged, immediately loaded implants) in the most precise way surface scan devices as used for digital impressions for crowns or implant abutments will be applied and evaluated with metrology and 3D inspection software.

By achieving precise measurements, former studies could be revised or confirmed. Additionally we will get more data about marginal bone remodelling through a withinpatient comparison of transgingival and submerged healed implants.

8. Risks and benefits of the investigational device and the clinical trial

8.1. Anticipated/predicted clinical benefit

The anticipated clinical benefits are precise three-dimensional measurements of marginal bone level changes at dental implants 4 months after insertion for different healing protocols. In this time the implants should reach the final osteoadaptive phase in which a steady state resorption remodelling sequence is achieved (Arun K. Garg 2010). We anticipate significant differences in marginal bone resorption according to the performed healing protocol. The benefit of an withinpatient comparison is that all three healing protocols take place in the same preconditions.

Patients who wish for an implant-supported superstructure (fixed or removable) with six implants are eligible for the trial. Recent publications show good results for the use of six implants, with the possible advantages of a better aesthetic and functional rehabilitation (Kern et al).

8.2. Anticipated/predicted adverse effects of the device

The therapy-related risks of implant surgery are equivalent in all individuals. There are only standard therapy-related costs for the patients, which correspond to the normal range.
Like any surgery, dental implant surgery poses some health risks. Problems are rare, though, and when they do occur they're usually minor and easily treated.
Risks include:

- Infection at the implant site
- Injury or damage to surrounding structures, such as other teeth or blood vessels
- Nerve damage, which can cause pain, numbness or tingling in your natural teeth, gums, lips or chin
- Allergic reaction on medication
- Periimplantitis and implant loss

8.3. Risks associated with the investigational device itself

All three healing protocols (submerged, transgingival healed and immediately loaded implants) are integrated in the prosthetic treatment for different indications yet there is a lack of precise data about the bone remodelling and marginal bone loss in dependence of the different healing protocols.
In immediately loaded Implants and transgingival healed implants there is a higher risk of early plaque adhesion and periimplant infection. Immediately loaded implants need more primary stability to absorb the forces transferred by the prosthesis. Due to the early loading there is a risk of increased marginal bone loss whereas the benefits are a faster prosthetic treatment.

8.4. Risks associated with participation in the clinical trial

The additional risks associated with the participation in this clinical trial are the manageable complications that could occur during the Implant exposure procedure in which the incision is extended to a full thickness flap for precise measurements of the marginal bone level.

Interactions among the three different methods with resulting impacts on the implants are unlikely: Non-loaded implants are protected against acting forces by means of the bar-supported superstructure. Also the implants are placed in their respective positions with a 3-4 mm distance apart from each other, which prevents impacts of the loaded implants on the neighboring ones.

In case of an implant loss an additional surgical intervention will be required in order to remove the implant. A renewed insertion is possible in many cases.
A removal or renewed insertion of the implant would not result in any additional costs for the patient.

8.5. Potential interactions with simultaneously administered medical treatments

Standard pain medication and antibiotics will be used in this trial. Possible interactions will be taken in consideration at the first visit by analysing the health history questionnaire and anamnesis.

8.6. Justification for the risk-benefit assessment

The benefits for the patients are well attached dental prosthesis to implants one week after implant insertion which lead to improved appearance, speech, comfort and easier eating. At the end of the study all 6 implants can be used as anchors for a prosthetic treatment which opens all different varieties of prosthetic possibilities tailored for the patient’s needs.

9. Aims and hypotheses of the clinical trial

9.1. Primary and secondary aims

The main objective of the study is to measure the marginal bone level changes at dental implants for different healing protocols (transgingival, submerged, immediately loaded implants) in the first 4 months of osseointegration.
Therefore, the bone level will be measured in relation to the implant margin. In former studies these measurements have been performed using a probe (Lorenzoni et al. 2003). Using an intraoral bone-surface scan provides more precise and reproducible results.
As a secondary objective the patients comfort and acceptance of the surgical procedure should be determined.

9.2. Primary and secondary hypotheses

Specifically, the following questions should be answered in this clinical trial:

- Are there differences in periimplant bone remodelling between the submerged, transgingival healed non-loaded implants and immediately loaded implants within the first 4 months of osseointegration?
- Are there differences in periotest or ISQ values between the submerged, transgingival healed non-loaded implants and immediately loaded implants within the first 4 months of osseointegration?
- Are there differences in survival rate between the submerged, transgingival healed non-loaded implants and immediately loaded implants within the first 4 months of osseointegration?
- Are there differences between the different measurement methods (X-rays versus Probing versus Surface Scans)

9.3. Alleged and foreseen benefits of the investigational device

We anticipate significant differences in marginal bone resorption according to the performed healing protocol. The benefit of a withinpatient comparison is that all the healing protocols take place in the same preconditions.

By receiving more precise data about bone remodelling for the different healing protocols, indications could be re-evaluated or extended.

9.4. Risks and predictable adverse effects of the device

The possible higher marginal bone level changes at immediately-loaded or transgingival healed non-loaded implants will be evaluated. This could lead to re-evaluation of therapeutic options and improvement of prosthetic treatment

10. Structure of the clinical trial

10.1. General information

This follow-up-study is a controlled clinical pilot trial and is conducted according to international standards of Good Clinical Practice and the current version of the Declaration of Helsinki (ICH-GCP Guidelines).

The objective is to evaluate the differences of the survival rate, measurements of Implant stability values, biologic and prosthetic complications, the patients satisfaction and periimplant bone loss in a within patient design for immediately loaded, non-loaded submerged and non-loaded transgingival healed implants within the first 4 months of osseointegration.

In former studies the measurements of bone remodelling in the different healing protocols of dental implants have been performed using a probe (Lorenzoni et al. 2003). By obtaining intraoral scans we aim to receive more precise and reproducible results of the bone level.

In twenty patients with edentulous mandibles six implants (Astra EV) will be placed in the interforaminal region of the lower jaw located at positions 34, 33, 32, 42, 43, 44.

Measurements of Implant stability values, X-Rays and the first bone-surface scan will be performed immediately after the insertion of the implants using CEREC Omnicam (Dentsply Sirona). Scan-bodies will be used to acquire comparable data serving as reference data. Additionally to the surface scan, conventional impressions will be made using transfer copings on positions 33 and 43 and polyether Aquasil (Dentsply DeTrey) to acquire models to manufacture Dolder Bars for immediate loading.

The Implants on positions 34 and 44 will be left submerged and the implants on positions 32 and 42 will be left for transgingival healing.

Within a period of 7 days of manufacturing process, a Dolder-bar with the full denture analogue will be integrated on the 2 implants at positions 33 and 43.

In a second-stage surgery after a healing period of 3-4 months the necessary access flap for exposing the remaining submerged implants will be expanded to a full thickness flap, exposing the margin of all involved implants in order to collect as much information as possible about clinical differences between loaded and non-loaded implants. The clinical parameters to be evaluated at this point will be: survival

rate and measurements of implant stability values after mounting the gingiva formers. Additionally a second bone-surface scan will be performed using CEREC Omnicam (Dentsply Sirona). Scan-bodies will be used to acquire a fixed reference and comparable data.

Both scans will be analysed using the Simplant-Software (Dentsply Implants). The bone contours of the surface scan images will be superimposed to measure the differences in three-dimensional space.

Clinical trials show evidently, that the bone loss measured by radiographs and by probing shows the highest bone resorption within the first three months after the insertion of dental implants. After three months a steady state, where no bone gain or loss can be measured, has been reached (Hermann et al. 2001; Brägger et al. 1998; Günther 2005; Siddiqui et al. 2001)

After contact with the implant the bone cells spread along the metal surface. This phase known as the Osteoconductive Phase continues over the first 3 months. At the time of 3-4 months after initial placement, the maximum surface area is covered by bone. The final Osteoadaptive Phase begins approximately 4 months after implant placement. It is associated with a steady state resorption remodeling sequence that continues after the implants are exposed and loaded (Arun K. Garg 2010).

GCP Statement: This study will be conducted in compliance with the principles of the Declaration of Helsinki, the ICH-GCP guidelines and in accordance with the relevant provisions of Austrian Medical Devices Act (MPG), the European Directive on implantable medical devices (90/385/EEC), the Styrian Hospitals Act (KALG), the Federal Law on hospitals (KAKuG), the EN-ISO standards 14155-1 and -2, EN ISO 14971, 10993 and all other ENISO eligible relevant legislations.

10.2. Devices and reference devices

Reference devices for the marginal bone remodelling are single tooth x-rays. These will be performed immediately after implant placement and 3-4 months after implant placement as a standard procedure in all kinds of implant placements. X-rays are a fast and common way to acquire information about the periimplant bone height. Nevertheless there might be limitations of this technique due to its two-dimensional character, its diffractions and possible distortions. As this is a standard procedure the exposure remains the same.

The device for the determination of the marginal bone remodelling is a digital impression using already said devices: scan bodies, intra-oral camera, and software.
Other devices that will be used in the study are:
Periotest (Medizintechnik Gulden) and Ostell ISQ measurement (Ostell AB) will be used as a source of excitation force to acquire the impact response of the implant.
Medication that will be used in our study includes common painkillers and antibiotics.

10.3. Test persons

10.3.1 Inclusion Criteria:

Patients fulfilling all of the following inclusion criteria may be enrolled in the study:

- capability of giving an informed consent
- good health as defined by the subjects medical history (no contraindications as described in the exclusion criteria below)
- age 20 to 80 years
- Patients who require 6 implants in the positions 32, 33, 34, 42, 43, 44
- edentulous mandible with enough interforaminal bone volume for placement of 6 implants
- Residual vertical bone height of at least 8mm in the interforaminal region
- Patients who wish an implant-supported restoration with six implants

10.3.2 Exclusion Criteria:

The presence of any one of the following exclusion criteria will lead to exclusion of the subject:

- Homelessness
- Smoking
- Medication with a contraindication for implant therapy
- Skeletal immaturity
- Any active malignancy or ongoing treatment for malignancy
- An active infection at the operative site

- Persistent compartment syndrome or neurovascular residua of compartment syndrome
- Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone
- Contraindications to the class of devices under study, e.g. known hypersensitivity or allergy to class of devices
- Pregnancy
- Intention to become pregnant during the course of the study
- Breast feeding
- Lack of safe contraception
- Medication for anticoagulation with INR > 2
- Patients with an elevated bleeding risk

Participation in this study is performed for patients on a voluntary basis. The patients give consent to the use and interpretation of the resulting data.
The therapy-related risks of implant surgery are equivalent in all individuals. There are only standard therapy-related costs for the patients.
Individual patient identification numbers are assigned according to the time of entry into the study. On termination of a patient from the study another participants must be included so that the minimal number of participants does not fall below 20.

10.3.3 Patient numbers:

All patients who meet the study inclusion criteria will be given a unique study identification number (patient ID).

10.3.4 Criteria and procedures for the withdrawal of test persons or termination of the trial.

Termination of the trial for a proband (drop-out):
The following events lead to a withdrawal of a study participant after the initial inclusion to the investigation:

1. Finding of an incorrect inclusion during the study integration of the trial subject
2. Exitus before the last visit

3. No participation at the last visit within the prescribed time frame
4. Failure to meet the mandatory protocol requirements
5. Failure to collect at least one of the specified parameters and tests at any time of investigation
6. Deviations from the intended time periods
7. Incorrect test participant selection
8. Withdrawing consent for study participation by the candidates

When a subject withdraws after implant placement and the second surgery for the exposure of the remaining implants, the subject will be withdrawn from the study and replaced. The patient will have a final physical examination by the investigator. The obtained data of all withdrawn subjects will be analyzed.

The reasons for the withdrawal of a subject must be recorded in the log. The study is continuing with the next participant's identification number.

Termination of the entire trial:

A termination of the study may take place after consultation between the following Parties: Investigators, Ethics Committee

The investigator may cancel the study at any time for the benefit and in the interest of the participants, if severe adverse reactions or other unforeseen circumstances occur. In this case, the Ethics Committee will be informed.

10.3.5 Time point of admission.

Patients who already decided on an implant-supported superstructure with six implants independently from this study are eligible for the trial.

All patients that fulfill the inclusion criteria and want to participate at the trial will be given a patient information leaflet and will be able to give the informed consent on a separate agreement form. Admission to the trial starts at Visit 1 when the patients will be again informed about the course of the study, the procedures and examinations. There will be enough time for the patients to reconsider their entry into the trial.

10.3.6 Anticipated total duration of the clinical trial.

The anticipated total duration of the trial lasts from inclusion of 20 patients until the last measurements performed on the surface scans. We assume the completion of the trial in Decembre 2018

10.3.7 Anticipated duration of the participation of each test person.

The total duration of the participation of each test person of the trial lasts from Visit 1 to Visit 8. That is the time after the implant exposure and the second surface scan. All necessary measurements will have been performed. After the suture removal, patients will be free to proceed with further prosthetic treatment.

10.3.8 Required number of test persons to be included in the clinical trial.

Based on the former study performed at our department (Lorenzoni et al. 2003) we performed a sample size estimation. A sample size of 8 in each group will have 80% power to detect a difference in means of -0,580 (the difference between a Group 1 mean, μ_1, of -0.910 and a Group 2 mean, μ_2, of -0.330) assuming that the common standard deviation is 0.380 using a two group t-test with a 0.05 two-sided significance level. When the sample size in each of the 3 groups is 9, a one-way analysis of variance will have 80% power to detect at the 0.05 level a difference in means characterized by a Variance of means of 0.060, assuming that the common standard deviation is 0,380.
Based on these statistical calculations and considerations on possible dropouts, a patient sample size of 20 was determined.

10.3.9 Estimated time required to obtain the stated number of persons (i.e., duration of recruitment).

10.4. Recruitment will take place until the required number of persons is reached. We estimate 1 year to obtain the necessary number of patients.**Treatments**

Visit 1: Patient recruitment and screening

20 patients requiring an implant treatment of the edentulous lower jaw will be included in the study in compliance with the above inclusion and exclusion criteria. All patients will be recruited from the regular pool of patients seeking implant therapy at the Dental School of Medical University of Graz.

No additional efforts for recruitment will be undertaken.

. Preoperative evaluation will include a complete medical history and a clinical and radiographic oral examination of the recipient site.

All patients will be given a patient information leaflet and will be able to give the informed consent on a separate agreement form.

During the first visit, about one week prior to the planned implant surgery, the participants will be informed about the course of the study, the procedures and examinations. The patient's history will be taken and the current health status recorded. All relevant demographic, medical and dental data of the patients will be recorded and the agreement to participate in the study will be obtained. For preoperative, radiological diagnostics (evaluation of mandibular, measuring the residual bone height) a panoramic x-ray will be performed.

Additionally the patients will fill out the OHIP-G 14 questionnaire to aquire information about the oral health-related quality of life of the patients as a baseline before the study. Intraoral Photographs will be taken.

Randomization and Blinding

Due to the prosthetic restoration and in order to prevent any acting forces on the neighboring implants it is not possible to perform randomization or blinding of neither the patients nor outcome assessors. The implants are always placed at the same position and the positions of the immediately loaded and non-loaded submerged and transgingival healed implants are predetermined.

Visit 2: Implant Surgery and first scan

At visit 2 a preoperative digital volume tomography will be performed.

All surgical procedures will be performed on an outpatient basis under local anesthesia under standard conditions in septic surgery. All patients will be advised to rinse for at least 1 minute with 0.2% chlorhexidine digluconate. Preoperatively, the surgical site will be evaluated. After preparation of a full thickness flap the bone will be assessed for quality and quantity.

All patients will receive CE-certified implants of the same company and with the same design used in the Department of Oral Surgery & Radiology and Division of Prosthodontics, Restorative Dentistry, Periodontology and Implantology, Dental

School at Medical University of Graz as standard implants, that are approved in Austria (ASTRA TECH® Implant System, Dentsply Implants).

The implants will be placed in the interforaminal region at positions 34, 33, 32, 42, 43, 44 with a minimum distance of 3 mm between each implant shoulder (Danza et al, 2011). The upper edges of the implants will be placed at the bone level and by achieving the necessary primary stability. After the implant placement any excessive bleeding will be stopped, by applying bone wax or cauterization. The bone level in relation to the implant margin will be scanned using CEREC Omnicam (Dentsply Sirona) and appropriate scan bodies will be used on all 6 implants to acquire a fixed reference for the later comparison on all 6 implants.

Additionally conventional impressions using Transfer Abutments and Aquasil (Dentsply DeTrey) will be performed for manufacturing of the dolder bars for immediate loaded implants on positions 33 and 43, and transgingivial healing abutments will be applied to the implants on positions 32, 33, 42, 43. The Implants on positions 34 and 44 will be left for submerged healing using cover screws.

Finally, the mucoperiosteal flaps will be adapted and sutured tightly. For post-operative, radiological diagnostics a panoramic x-ray and single tooth x-rays of all implants will be taken. The administration of antibiotics, anti-inflammatory or other accompanying medication will be documented. Intraoperative Photographs will be taken.

Visit 3: Integration of dolder bar to Implants 33 and 43

Maximal 72 hours after the implant placement, the manufactured dolder-bar will be integrated to the implants on positions 33 and 43 and the prosthesis will be adapted to fit. The patients' perception and acceptance will be assessed using the visual analog scale (VAS (Bijur, 2008)) assessing pain and swelling occurring after implant surgery. Intraoral Photographs will be taken.

Visit 4: Suture removal and integration of the dolder bars

Approximately to 7 days following the implant placement, all sutures will be removed and the patients' perception and acceptance will be assessed using the

visual analog scale (VAS) assessing pain and swelling occurring after implant surgery. Intraoral Photographs will be taken.

To evaluate the quality of life the OHIP-G 14 questionnaire will be filled out by the patients.

Visits 5-7: healing period

A four-month healing period of the implants follows. Regular clinical checks will be carried out at intervals of about 4-5 weeks with sensitivity tests, patient comfort tests (VAS) and questionnaires on general patient satisfaction (oral health impact profile: OHIP-G 14, (Slade 1997)). To evaluate the quality of life the OHIP-G 14 questionnaire will be regularly filled out by the patients

Visit 8: Re-entry surgery and second scan

All patients will be advised to rinse for at least 1 minute with 0.2% chlorhexidine digluconate.

In the second surgery, the exposure of the remaining implants on positions 34 and 44 will be performed by making a crestal incision. To perform the second scans the incision will be extended to a full thickness flap to evaluate the bone quality and quantity around all 6 implants. The bone level in relation to the implant margin will be scanned using CEREC Omnicam (Dentsply Sirona) and appropriate scan bodies will be used on all 6 implants to acquire a fixed reference for the later comparison on all 6 implants. Intraoperative Photographs will be taken.

One week (7 - 9 days) following implant exposure, all sutures will be removed and each patient’s perception and acceptance will be assessed using visual analog scale (VAS) assessing pain and swelling occurring after implant surgery.

Subsequently to visit 7, all patients will undergo and continue their regular therapy. During this period, abutment connection, impression taking and various try-ins will take place until the insertion of the final reconstruction will be performed. Any adverse events occurring during this period will be recorded. To evaluate the quality of life the OHIP-G 14 questionnaire will be filled out by the patients

Visits 9-12 follow-up after implant placement

During the follow-up time regular radiological and clinical recall checkups will be carried out. Oral hygiene and periodontal or peri-implant conditions will be controlled and documented and professional tooth cleaning (scaling, root planing) will be performed in intervals adjusted to the patients' needs.

Radiographic check-ups will be scheduled 12 and 24 months after the first surgery. Standard x-rays and panoramic x-rays will be produced and any adverse events occurring during this period recorded.

Study Procedures

During the observation period, the implant survival rates will be levied, clinical and radiological controls will be carried out and the incidence of biological and technical complications will be documented. Furthermore, a questionnaire on general patient satisfaction will be completed (Oral health impact profile: OHIP-G14, (Slade 1997)).

1. Clinical evaluation

- Measurement of insertion-torque after the placing of implants
- Assessment of the stability of inserted implants by determining the Periotest and ISQ values:

  1. Immediately after the insertion
  2. During the postoperative visits
  3. After exposure of the implants 3-4 months after implant placement
- Investigation of patient satisfaction using a questionnaire (OHIP-G 14 (Slade 1997))
- Evaluation of patient’s perception/acceptance using a questionnaire with a scale ranging from 1 to 10, where 1 represents „no pain“ and 10 the „most painful“. The perception of pain and swelling will be assessed.
- Intra-oral photographs (frontal and profile view including a calibrated size mark) taken at determined time points at six study visits for documentation.
- Subjective assessment of the soft tissue by the study dentist according to the following four categories: normal, swollen, red, and dehiscence.
- Assessment of the extra-oral and intra-oral sensitivity by the study dentist according to two categories: regular and disturbed.

- Assessment of adverse events by the study dentist and by questioning the patient throughout the clinical examination.

2. Radiographic examination

- Standardized periapical radiographs serving as routine clinical assessment.
- Panoramic radiographs
  - Prior to implant surgery
  - Immediately after implant surgery as postoperative control
  - Immediately after second implant exposure surgery for postoperative control

3. Scan analysis

To be able to determine the change of bone quantity around loaded and non-loaded implants two different scans of the area with an intraoral scanner will be made.
The first scan immediately after the implant insertion and the second one four months after the insertion. As a reference scan-bodies applied to the implants will be used.
The scan-procedure will be performed according to the recommended protocol of Sirona Cerec
The two stl-data sets will be imported into the SIMPLANT (Dentsply Implants) software and matched with the optical scan modul.
The measurements between the reference points and the marginal implant bone next to unloaded or loaded implants will be documented.

11. Study Schedule

Study Period	**Screening**	**Treatment Period**					**Follow-up**			
Visit	**1**	**2**	**3**	**4**	**5-7**	**8**	**9**	**10**	**11**	**12**
Timeline	**-7d +-2d**	**0d**	**+Max 72 h**	**+7d +- 3d**	**+1,2,3m +-7d**	**+4m +- 7d**	**+4m +-7d**	**+6m +-10d**	**+12m +- 10d**	**+24m +- 10d**
Informed consent Health questionnaire, medical history Inclusion, exclusion criteria,	X									
Pregnancy test	X					X			x	x
OHIP-G 14	X			X	X		X		x	x
Implant surgery and first scan		X								
Suture removal				X			X			
Implant exposure and second scan						X				
Photographs	X	X	x	X		X	X			
Digital Volume Tomography		x								
Panoramic x-ray	X	X				X				

Single tooth x-ray, probing		X				X			x	x
Clinical evaluation			X	X	X	X	X	X	X	X
Conventional Impressions		X				X				
Periotest / ISQ-measurement		X			X	X		X	X	X
Implant exposure 32, 42		X								
Implant exposure 33, 43		X								
Implant exposure 34, 44						X				
Integration of dolder bars to implants on positions 33, 43			X							
Further Treatment for definitive prosthetic therapy							X	X	X	X

The use of three different implant healing protocols, the OHIP-G 14 questionnaire, the pregnancy testing and the intraoral camera scans are study-specific procedures while all other procedures are routine examinations.

11.1. Regulations for monitoring

The Principle Investigator consents to data evaluation being performed by the person in charge of monitoring in accordance with the monitoring plan, in order to ensure satisfactory data collection and adherence to the study protocol.
Furthermore, the Principle Investigator states that he/she is willing to cooperate with this person and shall provide this person with all required information whenever necessary. This includes access to all documents related to the trial, including study-relevant medical files of patients in original form. The tasks of the investigator include maintenance of these patients' medical files as comprehensively as possible; this includes information concerning medical history, accompanying diseases, inclusion in the trial, data about visits, results of investigations, dispensing of medication, and adverse events. The monitor will also be permitted to perform data evaluation and draw comparisons with the relevant medical files in accordance with the SOPs and ICH-GCP guidelines at predetermined intervals, in order to ensure adherence to the study protocol and continuous registration of data. All original medical reports required as sources for the information given in the CRF or the database shall be inspected. The study participants will have given their consent to such inspection by signing the consent form.
The person in charge of monitoring is obliged to treat all information as confidential and to preserve the basic claims of the study participants in respect of integrity and protection of their privacy.

11.2. Statistical considerations

Primary and secondary variables will be evaluated descriptive and explorative.
The difference in bone loss over 4 months will be calculated for the three treatment groups.

A linear mixed model will be applied to evaluate the influence of the treatment on the bone level after 4 months. Since there are 6 implants from one patient, the patients will be included as a random effect. Treatment group will be a fixed effect.

Based on our former study we performed a sample size estimation. A sample size of 8 in each group will have 80% power to detect a difference in means of -0,580 (the difference between a Group 1 mean, μ_1 of -0.910 and a Group 2 mean, μ_2 of -0.330) assuming that the common standard deviation is 0.380 using a two group t-test with a 0.05 two-sided significance level. When the sample size in each of the 3 groups is 9, a one-way analysis of variance will have 80% power to detect at the 0.05 level a difference in means characterized by a Variance of means of 0.060, assuming that the common standard deviation is 0,380.

Based on these statistical calculations and considerations a patient sample size of 20 was determined. All statistical calculations will be performed in a significance level of 5%. Possible Drop- outs will be replaced to reach the necessary number. There will be no interim analysis.

11.3. Data management

Numbered data collection protocols will be used for data collection. Each protocol will be provided with the individual study identification number of the patient. The logs will be completed legibly and clean with a ballpoint pen. Errors have to be crossed out and corrections will be provided with a date.

Clinical and radiological parameters

In the clinical examination, peri-implant parameters (probing depth / Bleeding on probing, Periotest / ISQ values) will be examined. The crestal bone level of the implants will be measured by means of single tooth x-rays and surface scans obtained with

CEREC Omnicam (Dentsply Sirona). The values at the time of implant insertion and the values four months after the implant placement will be documented and compared.
The secondary objective (compare safety and tolerability) will be measured by the following secondary endpoints:
Complications at suture removal and during the 4 moths healing period after the implant surgery: sensitivity (anaesthesia, paresthesia, hypo- or hyperesthesia), Adverse events will be recorded
Investigation of patient satisfaction will be carried out using a questionnaire for patient satisfaction (OHIP-G 14 (Slade 1997)).
A questionnaire will evaluate the patient's perception/acceptance using a scale ranging from 1 to 10, where 1 represents „no pain" and 10 „most painful". The perception of pain and swelling will be assessed.
The acquired digital data will be stored at a server computer at the Department of Dentistry and Maxillofacial Surgery with restricted access. Patient data will be stored using k-anonymization.

11.4. Modification of the study protocol

The vote of the ethics committee applies solely to the information contained in the application; it does not include extensions or modifications of the research project undertaken at a later point in time. In case of any modification, an amendment of the study protocol signed by the Principle Investigator is required. Any modification of the study protocol must be attached, as an amendment, to all study protocols in circulation. The ethics committee must be informed of all modifications in the study protocol. In case of modifications in the study protocol that are not merely of a formal nature but contain changes pertinent to the study participants, a renewed vote of the ethics committee must be obtained. If applicable, the patients/probands must be informed in the patient information and consent form about changes in the terms and conditions of the trial.
The authorities (BASG) also must be notified of changes in the study protocol. The appropriate reporting forms should be used for these notifications. This does not apply to clinical studies concerning medical device with the CE marking for the approved indication (§ 40, paragraph 4).

11.5. Deviations from the clinical study protocol

Any deviation from the clinical study protocol/CIP will be reported together with an explanation for the deviation. The reasons for withdrawal and discontinuation of any subject from the investigation will be recorded. If such discontinuation is caused by problems with safety or lack of effectiveness, that subject will be followed up in the investigation, if possible. The Ethics Committee will be informed.

11.6. Disposition statement for the investigational device

Access to the investigational device will be controlled. The investigational device will only be used in the clinical trial and in accordance with the CIP.

The sponsor will preserve all records that document the material site of all investigational device from a consignment of investigational device to the study sites until they are returned or disposed.

The Principle Investigator or an authorised representative will preserve records that document the receipt, usage, return, and disposal of the investigational device; the records must contain the following:

- Date of receipt;
- Identification of each investigational device (batch number/serial number or distinct code);
- Date of expiry if applicable;
- Date of use;
- Identity of the test person;
- Date of return of unused, expired or non-functioning investigational device, if applicable.

12. Legal principles

During the implementation of the trial, the (current versions of) following guidelines and laws must be followed in addition to the Declaration of Helsinki (such as):

• Current version of MPG (Austrian Act on Medical Devices)
• EN 14155
• ICH-GCP Guideline
• EU directives 90/385/EEC, 93/42/EEC, 98/79/EC etc.

12.1. Vote of the ethics committee

In accordance with § 57 MPG (Austrian Act on Medical Devices), the clinical trial may be started only after the competent ethics committee has issued its statement of approval and the appropriate authorities (BASG) have provided their non-prohibition/approval.
No reporting to, or approval of, the BASG is required for clinical trials concerning medical devices with CE marking, being used for the approved indication.

12.2. Procedure to obtain informed consent

The investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort that may entail. Each subject must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that the withdrawal of consent will not affect his/her subsequent medical treatment. The subject must be informed that his/her medical records may be examined by authorized individuals other than their treating dentist. All subjects of this study will be provided with an information sheet and a consent form describing the study and giving sufficient information to make an informed decision about their participation in this study.
The subject information sheet and the consent form will be submitted with the protocol for review and approval by the IEC for the study. The formal consent of each subject, using the IEC-approved consent form, has to be obtained before he or she is submitted to any study procedure. The subject has to read and consider the statement before signing and dating it, and has to be given a copy of the signed document. The consent

form has to be signed and dated by the investigator (or his designee) as well and it will be retained as part of the study records.

12.3. (Serious) Adverse events

12.3.1 Adverse events

An adverse event (AEs) is defined as any untoward medical occurrence in a subject or clinical investigation subject, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal study product, whether or not related to the medicinal study product. An AE may also relate to a new disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

AEs observed by the investigator and/or reported by the subject must be described in the CRF during the entire treatment period, regardless of the medicinal study product relation assessment. During the follow-up period study specific AEs will be observed and reported. For all AEs, sufficient information will be pursued and/or obtained so as to permit an adequate determination of the outcome of the event (i.e., whether the event should be classified as an serious advere event (SAE, see below) and an assessment of the casual relationship between the AE and the investigational device. Whenever available, the underlying disease or condition for which a therapeutic or diagnostic procedure is required should be reported as the AE term. Surgeries or other invasive procedures that have already been planned prior to the start of the study do not have to be documented as AEs. These planned procedures will have to be recorded in the CRF by the investigator at the baseline visit. It is not important if the condition has been known before enrolment, but if the procedure has been planned before. Pregnancy per se does not classify as an AE. However, AEs related to a pregnancy have to be reported like any other AEs. Pregnancy should be confirmed by a reliable laboratory test. Pregnant subjects must be immediately withdrawn from the clinical study.

12.3.2 Serious adverse event

An SAE is any untoward medical occurrence that at any dose

• causes death,or

• is life-threatening, or

• requires subject hospitalization or prolongation of current hospitalization, or

• results in persistent or significant disability/incapacity, or

• is a congenital anomaly/birth defect (In clinical trials, this refers to a congenital anomaly in an offspring of a subject or subject who received study device), or

• any important medical event, or

- and any other event which, though not included in the above, may jeopardise the subject or may require intervention to prevent one of the outcomes listed above.

Any other medically important condition that may not be immediately life-threatening or result in death or hospitalization but could jeopardize the subject or might require intervention to prevent one of the outcomes listed above should also be considered serious, based on medical and scientific judgment. Such conditions can include i.e. intensive self-indicated home treatment for allergic bronchospasm; certain laboratory abnormalities (e.g. blood dyscrasias); convulsions that do not result in hospitalisation; development of drug dependency or drug abuse.

12.4. Assessment of (Serious) Adverse Events

The investigator will promptly review documented AEs and abnormal test findings to determine if

• the abnormal test finding should be classified as an AE,

• if there is a reasonable chance that the AE was caused by the investigational device or study treatment(s), and

• if the AE meets the criteria for an SAE.

The assessment by the investigator with regard to the study device relation is done according to the following definitions:

Unlikely relation:

An AE, whose

• temporal relationship to device administration makes a causal relationship improbable and

• in which other drugs/devices or chemicals or underlying disease provide plausible explanations.

Possible relation:

An AE, which

• occurs within a reasonable time sequence to use of the device but

• could also be explained by concurrent disease or other drugs/devices or chemicals.

Information on device withdrawal may be lacking or unclear.

Likely relation:

An AE, which

• occurs within a reasonable time sequence to administration of the device,

• is unlikely to be attributed to concurrent disease or other drugs/devices or chemicals, and

• follows a clinically reasonable response on withdrawal (de-challenge).

Re-challenge information is not required to fulfil this definition.

Certain relation:

An AE, which

• occurs in a plausible time relationship to device administration and

• cannot be explained by concurrent disease or other drugs/devices or chemicals.

• The response to withdrawal of the device (de-challenge) should be clinically plausible.

The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Reporting obligations Sponsor:

Registration of all adverse events and adverse effects in accordance with § 42, paragraph 8 MPG.

Note reporting obligations in accordance with § 70.

MPG § 61 (1) The clinical investigator must inform the ethics committee about any subsequent modifications of the study protocol and all serious side effects that occur in the clinical trial. The reporting obligations under § 70 remain unaffected by this clause.

In accordance with § 61 (1) MGP the Principle Investigator is obliged to report, to the competent ethics committee, all serious adverse effects that occur during clinical studies.

MPG §2 (17): "Adverse effects" are defined as those undesirable accompanying effects that occur and are related to a medical device used in accordance with regulations.

The sponsor must report to the national competent authorities where the clinical investigation has commenced:

- for all reportable events which indicate an imminent risk of

death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. For all other events the sponsor must report to the competent authorities within 7 calendar days.

Reporting of SAEs to the BASG should be done by using form F_I208, which is available on the BASG- website under: http://www.basg.gv.at/medizinprodukte/klinische-pruefung-von-medizinprodukten/

Furthermore notification form F_I287 (SAE report table) has to be maintained for all SAEs occurring during the clinical trial (Line listings).

12.5. Publication policy

Authors will include all persons who contribute significantly to the result of this study.
The clinical trial will be registered in a publicly accessible database in order to publish the results in high ranked journals.
It is not planned to publish interim results or partial results.

13. References

Adell, R. et al., 1981. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. International journal of oral surgery, 10(6), pp.387–416.

Arun K. Garg, 2010. Implant Dentistry, 2nd Edition: A Practical Approach, Elsevier.

Becker, W. et al., 1997. One-step surgical placement of Brånemark implants: a prospective multicenter clinical study. The International journal of oral & maxillofacial implants, 12(4), pp.454–62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9274074.

Brägger, U. et al., 1998. Evaluation of postsurgical crestal bone levels adjacent to non-submerged dental implants. Clinical Oral Implants Research, 9(4), pp.218–224. Available at: http://dx.doi.org/10.1034/j.1600-0501.1998.090402.x.

Brugnami, F., Caiazzo, A. & Leone, C., 2009. Local intraoral autologous bone harvesting for dental implant treatment: Alternative sources and criteria of choice. Keio Journal of Medicine, 58(1), pp.24–28.

Danza M, Zollino I, Avantaggiato A, Lucchese A, Carinci F. Distance between implants has a potential impact of crestal bone resorption. The Saudi Dental Journal. 2011;23(3):129-133. doi:10.1016/j.sdentj.2011.02.002.

Chiapasco, M. et al., 1997. Implant-retained mandibular overdentures with immediate loading. A retrospective multicenter study on 226 consecutive cases. Clinical oral implants research, 8(1), pp.48–57.

Ericsson, I. et al., 2000. Early functional loading of Brånemark dental implants: 5-year clinical follow-up study. Clinical implant dentistry and related research, 2(2), pp.70–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11359266.

Günther, T., 2005. „Einflüsse prothetischer Versorgungen von Einzelzahnimplantaten des ITI Typs auf Osseointegration und Knochenverlust.“ Eine retrospektive Studie. Medizinische Universität Hamburg.

Hermann, J.S. et al., 2001. Biologic Width around one- and two-piece titanium implants. Clinical oral implants research, 12, pp.559–571.

Kern J-S,. Kern T., Wolfart S., Heussen N. , 2016. A systematic review and meta-analysis of removable and fixed implant-supported prostheses in edentulous jaws: post-loading implant loss. Clin. Oral Impl. Res, 27, pp. 174–195.Lorenzoni, M. et al., 2003. In-patient comparison of immediately loaded and non-loaded implants within 6 months. Clinical oral implants research, 14(3), pp.273–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12755777.

Schulte, W. & Lukas, D., 1993. Periotest to monitor osseointegration and to check the occlusion in oral implantology. The Journal of oral implantology, 19(1), pp.23–32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8246291.

Siddiqui, a a, Ismail, J.Y. & Kukunas, S., 2001. Immediate loading of dental implants in the edentulous mandible: a preliminary case report from an international prospective multicenter study. Compend Contin Educ Dent, 22(10), pp.867–70, 873–4, 876 passim; quiz 884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11915636.

Slade, G.D., 1997. Concepts of Oral Health, Disease and the Quality of Life. Measuring Oral Health and Quality of Life, p.172.

Tarnow, D., Emtiaz, S. & Classi, A., 1997. Immediate loading of threaded implants at stage 1 surgery in edentulous arches: ten consecutive case reports with 1- to 5-year data. Int J Oral Maxillofac Implants, 12, pp.319–324.

14. Signatures

By signing this document I confirm that the trial shall be performed in accordance with ICH-GCP, the Declaration of Helsinki, national laws, and the current study protocol.

Sponsor or his representative

Name, First name (in block letters)	**Date, Signature**

Principle Investigator

I confirm herewith that I have read and understood the present study protocol, and acknowledge all parts of it. I promise to ensure that the persons introduced in the trial at my centre shall be treated, observed and documented in accordance with the terms and conditions of this study protocol.

Name, First name (in block letters)	**Date, Signature**