Clinical Trial Protocol in consideration of ISO 14155

Comparison of customized allogenic versus autogenous bone block graft for alveolar ridge augmentation: a multicenter randomized controlled trial

Sponsor

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List of abbreviations

CIP	**Clinical Investigation Plan**
FPFV	**First Patient First Visit**
LPLV	**Last Patient Last Visit**
BASG	**Bundesamt für Sicherheit im Gesundheitswesen (Federal Agency for Safety in Healthcare**
AE	**Adverse Event**
SAE	**Serious Adverse Event**
IEC	**Independent Ethics Committee**
GBR	**Guided Bone Regeneration**
PROM	**Patient Reported Outcome Measures**

The clinical trial is conducted in consideration of ISO 14155 - Clinical investigation of medical devices for human subjects — Good clinical practice

Responsibilities and addresses

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Synopsis (in an official Union language determined by the Member State concerned)

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Name	Comparison of customized allogenic versus autogenous bone block graft for alveolar ridge augmentation: a multicenter randomized controlled trial
Running head	IndiALLO
Target population (or indication)	Partially edentulous patients in need of implant therapy and presenting an insufficient bone volume (horizontal ridge width <5mm) to allow placing a standard diameter implant defect-free in a prosthetically ideal position will be included
Study design	Randomized, controlled, multi-center clinical trial
Aims of the clinical trial	Primary aim of the trial The aim of this study is to evaluate whether allogenic and autogenous bone block alveolar ridge augmentations will result in comparable 3-dimensional clinical augmentation, radiological augmentation, new bone formation and % of contact area of new bone to bone graft six months post-surgery. Secondary aims of the trial I. To assess and compare the two block grafts in terms of safety, biocompatibility, complications and patient reported outcomes (PROMs) 4 months following surgery. II. To investigate the condition (health/disease) of dental implants 1 year after 2nd stage surgery and yearly and up to five years after bone augmentation
Outcome measures (endpoints) of the	Primary outcome measure

clinical trial	- Clinical bone ridge width gain - Radiological bone ridge width gain Secondary outcome measures - Histometric and histomorphometric assessment of the grafted site - Intraoral ridge profile change - Complications and adverse events - Patient related outcomes - Clinician related outcomes
Number of patients	26
Time schedule	*With reference to the trial* *Recruitment period:2 years* *Planned start (FPFV): January 2025* *Planned end (LPLV): August 2032* *With reference to patients* *Duration of treatment: active phase 10 months*
Inclusion criteria	• 1-4 missing teeth that need to be replaced with dental implants • Bone ridge width insufficient for dental implant placement; <5 mm of width as measured in a cone beam computed tomography at the ideal prosthetic position • Medically healthy with no known allergies to antibiotics • Non-smoker or light smoker (< 10) or previous smoker who had quit for 5 years or more • Periodontal health, as confirmed by clinical examination (Full mouth bleeding score and full mouth plaque score < 25%) and at least one neighboring natural tooth to the defect site(s) • Age of 18 or above

Exclusion criteria	• All contraindications against implant treatment or augmentative procedures (e.g., advanced systemic diseases, corticosteroid medication, immunodeficiency, pregnancy, intention to become pregnant, breastfeeding, lack of safe contraception) • Treatments or diseases that may have an effect on bone turnover or the bone itself or non-mineralized tissue metabolism (e.g., bisphosphonates or local radiotherapy, skeletal immaturity) • Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone diseases • Any active malignancy or patient undergoing treatment for a malignancy
	• Contraindications to the class of drugs under study, e.g., known hypersensitivity or allergy to class of drugs or the investigational product • Persistent compartment syndrome or neurovascular residua of compartment syndrome
Investigational bone graft and optional additives:	Botiss maxgraft® bonebuilder (botiss biomaterials GmbH) MinerOss® A (Alltec Dental GmbH) Argonaut® (Alltec Dental GmbH)
Treatment plan	**P (patient):** partially edentulous patients in need of implant therapy and presenting with an alveolar ridge width < 5mm **I (intervention):** individualized allogenic bone block alveolar ridge augmentation **C (comparison):** autogenous bone block alveolar ridge augmentation **O (outcome):** alveolar bone ridge width gain (clinical/intraoperative)

1. Scientific background

Increase in implant placement and need for bone augmentation

Over the past 20 years the treatment with dental implants has become increasingly important in the routine therapy of patients with tooth loss. It is evident that general dentists, periodontists, oral surgeons and oral maxillofacial surgeons are routinely using surgical techniques to augment the atrophic or residual alveolar ridges in adjunct with different materials [2]. Interestingly, in Germany in particular, there is evidence that oral and maxillofacial surgeons may be keener in the use of block grafting for both single and multiple implant treatment compared to oral surgeons[3]. However, based on the previous survey, both specialties seem to use a broad range of materials and techniques with blocks being rather popular.

One of the important factors to ensure long-term implant stability is both bone quantity and quality[4-6]. Due to trauma, pathologic- or natural processes (i.e., post-extraction) there is a frequent need for alveolar ridge augmentation with the use of bone grafts, other biomaterials and occasionally biologic agents. In the event of tooth loss, resorption of underlying bone appears most rapidly within the first year after the event, 40%-60% bone loss emerges within the first three years. In spite of the development of diameter-reduced implants and shorter implants, in order to enable ideal implant stability and hence, clinical success, a large number of patients still require alveolar ridge augmentation procedures. Bone grafts are necessary to promote bone regeneration, adequate primary implant fixation and osseointegration. As type of bone grafts are concerned there is a variety of options available: autogenous bone, allogenic bone, xenogeneic bone and alloplastics can be used to enhance bone quantity and help regenerate new bone. Currently, there is a significant amount of evidence hinting that autogenous bone grafts could be the gold standard due to their osteoconductive and osteoinductive characteristics [7]. The promotion of stem cells and the contained growth factors make autogenous bone grafts exceptional[8,9] but the ideal material which will balance the resorption and the complete replacement with new bone is yet to be discovered. In addition,

the factors regarding optimal outcome after ridge augmentation may be subject to what is the anatomy of the area, the objective of the augmentation and a series of patient related factors. Therefore, to find this balance of resorption and new bone formation a large variety of alternatives have been developed such as hydroxyapatite, calcium sulfate bio-ceramic biomaterials, deproteinized bovine bone or human-derived allogenic bone[10-12].

Bone grafting with customized allografts

The use of allografts is one of the most frequently applied alternatives to the acclaimed gold standard[12] or simply to what dentists are aware of or accustomed to[10]. Allografts have become more and more popular particularly in the United States, where about one third of all bone grafts used in orthopedic procedures are allogenic bone grafts[13] and this trend can also be partly extrapolated in the oral surgery [10] although a clear consensus is lacking[14,15]. Allografts are not only easy to handle and trim during surgery but they show excellent histological results [16-18] and

no apparent difference in the implant failure rate and implant success[14,19]. Additionally, in the benefits of allogeneic bone blocks it may be included their unlimited supply, absence of morbidity for the donor site (swelling, pain) and minimal safety concerns nowadays[20]. A recent systematic review compared radiological and histological outcomes after using a GBR approach or simply grafting with a block allograft (no membrane) versus the use of autografts for the alveolar ridge augmentation until today (Antonoglou et al. unpublished). In the above review a total of 13 comparative studies were included. Eight studies compared allograft blocks with autograft blocks, 4 compared xenograft blocks with autograft blocks and 1 compared two different allograft blocks. Direct and indirect radiographic comparisons were possible only amongst non-randomized studies. Direct comparisons of xenograft with autograft showed no

substantial difference in height change (-0.05 mm). Radiographic area change favoured autograft against allograft with 9.15 mm^2 less reduction during healing.

The review concludes that radiological resorption indicates that allografts might resorb at a higher and xenografts at a lower rate compared to autografts. Histological comparisons between autograft and allograft showed possible superiority of the autograft blocks in terms of reduced necrotic bone tissue and residual grafted material. The studied grafts used with conventional techniques, however, show low complication rates and an acceptable tissue quality in the augmented area at the end of the healing period. One trial that compares very closely with the suggested research has been conducted by Thoma and co-workers at the University of Zurich.

In this study they did not obtain histological specimens and focused on dimensional changes. Both xenograft and autograft increased the ridge width to a comparable extent. The shrinkage during the healing period did not differ substantially between the two groups. and the impact of hard tissue augmentation on the soft tissue contour was minimal.

Until today, there is neither an RCT nor a multicenter study investigating the previous outcomes, i.e. radiological and histological, simultaneously.

Today, with cone-beam computed tomography there is a possibility to visualize the alveolar bone defects and customize allogenic bone blocks. In addition, the use of customized allogenic bone blocks for bone augmentation could be a potential and convenient alternative to the use of blocks with standard dimensions.

The objective of the present trial will be to show that these customized allogenic block grafts behave equally well compared to autogenic block grafts investigating clinical, radiological and histological, and additional patient related outcomes in a non-inferiority multicenter randomized controlled clinical trial.

The significance of this trial may be summarized in that it could suggest an affordable and user-friendly substitute to autogenic block grafting used in alveolar ridge augmentation surgery.

2. Name and description of the investigational bone graft

Investigational bone graft Botiss maxgraft® bonebuilder (allogenic bone block), optional addition of MinerOss® A (allogenic bone granules), covered with Argonaut® (porcine collagenbased membrane).

Step by step – customization process

1. Data upload
2. Block design
3. Design check of the 3D-planning
4. Order of allogenic bone block
5. Production

Duration of administration: One-time application at augmentation surgery.

Due to the stable trabecular structure of the cancellous bone, maxgraft® bonebuilder provides an ideal matrix for predictable and highly effective revascularization, rapid formation of new bone tissue and complete bone remodeling. Simultaneously the excellent biological regeneration capability of maxgraft® is supported by exceptionally good flexibility on the basis of natural collagen content, which will facilitate screw fixation. The processing sequence meets highest quality standards with regard to biomechanical properties and safety, prohibiting infect transmission or antigenic effects. It is storable at room temperature for 5 years. However, it should be used as soon as possible after delivery to provide a precise fit, enabling rapid revascularization and fast graft incorporation.

3. Rationale for the structure of the clinical trial

There are a lot of studies about the products and procedures. However, there is no direct comparison of autogenous and allogenic bone blocks regarding safety, biocompatibility, complications and patient reported outcomes (PROMs) 4 months following surgery.

4. Risks and benefits of the investigational bone graft and the clinical trial

Allografts are not only easy to handle and trim during surgery but they show excellent histological results [16-18] and no apparent difference in the implant failure rate and implant success[14,19]. Additionally, in the benefits of allogeneic bone blocks it may be included their unlimited supply, absence of morbidity for the donor site (swelling, pain) and minimal safety concerns nowadays[20]

4.1 Risk management

All implants and biomaterials will be applied according to the manufacturer's recommendation. Patients will frequently be examined for any side effects of the treatment. Standard treatment solutions in the case of occurring complications will be performed as a clinical risk management.

5. Aims and hypotheses of the clinical trial

Primary objective:

The aim of this study is to evaluate whether allogenic and autogenous bone block alveolar ridge augmentations will result in comparable 3-dimensional clinical augmentation, radiological augmentation, new bone formation and % of contact area of new bone to bone graft six months post-surgery.

Secondary objectives:

I. To assess and compare the two block grafts in terms of safety, biocompatibility, complications and patient reported outcomes (PROMs) 4 months following surgery.

II. To investigate the condition (health/disease1) of dental implants 1 year after 2nd stage surgery and yearly and up to five years after bone augmentation.

6. Structure of the clinical trial

6.1 General information

Study design: Randomized, controlled, multi-centre clinical trial

Study Duration: 7 years and 10 months (94 months)

All patients will be randomly assigned using a modified permuted block randomization approach in two groups using Randomizer Version 2.2.0 (www.randomizer.at).

(a) control group: autografts

(b) test group: customized allogenic grafts

6.2 Bone graft and optional additives

Study commercial Products:

Botiss maxgraft® bonebuilder	(botiss biomaterials GmbH)
MinerOss® A	(Alltec Dental GmbH)
Argonaut®	(Alltec Dental GmbH)

6.3 Test persons

Partially edentulous patients in need of implant therapy and presenting an insufficient bone volume (horizontal ridge width <5mm) to allow placing a standard diameter implant defect-free in a prosthetically ideal position will be included.

The PICO framework for the present trial is designed as follows:

P (patient): partially edentulous patients in need of implant therapy and presenting with an alveolar ridge width < 5mm

I (intervention): individualized allogenic bone block alveolar ridge augmentation

C (comparison): autogenous bone block alveolar ridge augmentation

O (outcome): alveolar bone ridge width gain (clinical/intraoperative)

Inclusion criteria

Bone ridge width insufficient for dental implant placement; < 5mm of width as measured in a cone beam computed tomography at the ideal prosthetic position

Medically healthy with no known allergies to antibiotics

Non-smoker or light smoker (< 10) or previous smoker who had quit for 5 years or more

Periodontal health, as confirmed by clinical examination (Full mouth bleeding score and full mouth plaque score < 25%) and at least one neighbouring natural tooth to the defect site(s)

Age of 18 or above

Exclusion criteria

Contraindications against implant treatment or augmentative procedures (e.g., advanced systemic diseases, corticosteroid medication, immunodeficiency, pregnancy, intention to become pregnant, breastfeeding, safe contraception)

Treatments or diseases that may influence bone turnover or the bone itself or non-mineralized tissue metabolism. (e.g., bisphosphonates or local radiotherapy, skeletal immaturity).

Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone diseases.

Any active malignancy or patient undergoing treatment for a malignancy

Contraindications to the class of drugs under study, e.g., known hypersensitivity or allergy to class of drugs or the investigational product

Persistent compartment syndrome or neurovascular residua of compartment syndrome.

The anticipated total duration of the clinical trial is **94 months** with an **active phase of 10 months**. The estimated time required to obtain the stated number of persons is **24 months**.

6.4 Treatments

Augmentation surgery

Prior to the start of the surgery, patients will rinse with 0.2% of chlorhexidine and receive a perioperative antibiosis. The area/areas intended for surgery will be carefully anaesthetized.

Recipient site preparation: A paracrestal incision placing the line of incision towards the oral aspect of the ridge will be applied. Oblique releasing incisions will be used to allow for a wide flap basis as well as sufficient access to the defective ridge area. Any soft tissues remaining on the crest were meticulously removed and the ridge width will be measured. The cortical bone plate will be perforated at numerous locations symmetrically distributed across the area of the defect with a bur (round carbide bur, 1,4 mm).

Donor site preparation (control only): Depending on the size of the ridge defect (recipient site) and the donor site anatomy, the blocks will be harvested from the mandibular symphysis or the retromolar area. A mucoperiosteal flap will be elevated at the donor site, followed by preparation with a fissure bur or a piezo device and careful block graft mobilization 26.

Ridge augmentation at recipient site: In the test group, the customized allograft block:

Based on CT/CBCT scans of the patient, the allogenic bone block has already been virtually designed using 3D CAD/CAM technology prior to surgery. Manual adjustment of the block during the operation is rarely required. The allogenic block may be applied directly onto the defect, reducing the risk of infection as well as surgery time. The individual design provides a precise fit between local bone and the allogenic bone block, enabling fast graft incorporation and rapid revascularization.

In the control group, the blocks will also be adapted to the defect site morphology. With a small drill, holes for fixation will be prepared and the bone blocks will be immobilized with one or two screws. Subsequently, a layer of bone particles will be applied if needed to cover the autogenous bone and to fill up voids.

The obtained ridge width will be again measured before application of the membrane. In both groups, the collagen membrane will be trimmed to extend the augmented area 2-3 mm onto the intact bony borders of the defect. The membrane will be fixated using resorbable fixation pins. Tension free wound closure will be obtained through releasing incisions in the periosteum. A horizontal mattress suture and further single interrupted sutures will be placed intending a primary wound closure in both groups.

All patients will receive analgesic and anti-inflammatory medications and will be instructed to rinse with chlorhexidine (Chlorhexamed FORTE alkoholfrei 0.2%). Subsequently, penicillin will be given for 4 consecutive days. Temporary removable partial dentures will be carefully checked and adapted if necessary, to avoid trauma to the surgical area.

All patients will be asked to fill out VAS forms for the assessment of bleeding, swelling, pain and bruising for the following 7 days. The levels of each parameter will be marked by the patient on the form from 0 (e.g. no swelling) to 10 (e.g. very severe swelling). Compliance in completing the records of VAS and analgesic consumption forms will be monitored at the follow-up visits.

All sutures will be removed 7 days following augmentation surgery.

Implant placement and Re-entry (at 6 months post augmentation)

Six months following ridge augmentation, re-entry surgery and implant placement will be performed: Before surgery a CBCT scan will be conducted. After rinsing with chlorhexidine (Chlorhexamed FORTE alkoholfrei 0.2%) for one minute and application of local anaesthetics,

flaps will be raised to visualize the augmented ridge and the ridge width will be measured by means of a caliper to assess the oro-facial bone width to the nearest millimeter at the prospective implant. A hard tissue biopsy will be obtained in the prospective implant position by means of a trephine bur with an inner diameter of 1.8 mm. Subsequently, implants will be placed according to the manufacturer's instruction and in a prosthetically ideal position. Additional GBR procedures will be performed in case of dehiscence or fenestration defects at the implants. Flaps will then be adapted to allow a submerged healing of the implant.

After the implant placement post-operative occlusal photographs and a CBCT scan will be taken. All patients will be asked to use 0.2 % chlorhexidine mouth rinse twice daily until suture removal 7 days after implant placement.

Furthermore, post-operative occlusal photographs will be taken.

Flowchart of study procedures:

Visits	**Visit 1** Screening	**Visit 2** Augmentation	**Visit 3** Suture removal	**Visit 4** Implantation	**Visit 5** Suture removal	**Visit 6** 2nd stage surgery	**Visit 7** Crown insertion	**Visit 8** Followup	**Visit 9** Followup	**Visit 10** Followup	**Visit 11** Followup	**Visit 12** Followup
Day/months/years		0	+7 days	+6 months = 180 days past augmentation	+6 months and 7 days	+10 months =300 days past augmentation =120 days past implantation	2-4 weeks after 2nd stage surgery	1 year after 2nd stage surgery	2 years after 2nd stage surgery	3 years after 2nd stage surgery	4 years after 2nd stage surgery	5 years after 2nd stage surgery
Informed consent	›											
Demographics	›											
Medical history	›											
In/Exclusion criteria	›											
Pregnancy test	›	X		X				X	X	X	X	X
Photographs	›	X	X	X	X	X	X	X	X	X	X	X
Impression	›		X		X		X	X		X		X
Clinical examination	›							X	X	X	X	X
Randomization	›											
Cone Beam CT	›	nach Augmentation		Vor Implantation				›	›	›	›	›

		X		X nach Implantatio X								
OPG	›											
Augmentation surgery		X										
Administer study medication		X		X								
Suture removal			X		X							
Implant placement				X								
Adverse events/study specific adverse events		X	X	X	X	X	X	X	X	X	X	X
PROMs			X									

7. Statistical considerations

The sample size calculation was performed with nQuery 8

When the sample size in each group is 13, a two group one-sided 0.025 significance level t-test will have 80% power to reject the null hypothesis that the test group (allogenic bone blocks) and standard (augogenous bone blocks) are not non-inferior (the difference in means, μT-μS, is 3.0 or farther from zero in the same direction) in favor of the alternative hypothesis that the means of the two groups are non-inferior, assuming that the expected difference in means is 0.63 and the common standard deviation is 2.0.

The primary endpoint in the initial trial will be sufficient intraoperative bone ridge width.

8. Data management

The inquiry, circulation and storage of personal data will be accomplished according to the data privacy act

After termination of the study all documents will be stored in the archive of the Department of Dental Medicine and Oral Health for 15 years.

The data will be captured into Excel (Microsoft Corporation, Redmond, Washington, USA). Mean, standard deviations (SD), medians, quartiles and min/max will be derived for continuous variables and counts for categorical data. Intergroup comparisons will be tested by a two-sided Wilcoxon–Mann–Whitney test because of the small sample size, and the nonnormality of the data and intra-group comparisons will be performed with Wilcoxon-signed rank test for continuous variables. All categorical variables will be tested with Chi-squared tests or Fisher's exact test.

The primary endpoint will be the clinically evaluated ridge width. To allow commenting on the possible equivalence of the two groups, the 90% confidence intervals will be provided in addition. The significance level will be set at 5%. No correction for the multiple testing for the secondary endpoints will be applied. We will perform sensitivity analyses to include centre and defect dimensions effects, dimensions of keratinized mucosa and different methods for handling missing data. R (version 2.15.0) will be used for all statistical analyses.

Additionally, regarding outcomes which will be collected repeatedly in time such as peri/implant clinical measurement a general linear model (GLM) for repeated measures will be used and evaluate the effect of test and control treatment on them.

This trial will be registered with the European platform for trial registration (https://www.clinicaltrialsregister.eu).

9. Modification of the study protocol

The vote of the ethics committee applies solely to the information contained in the application; it does not include substantial extensions or modifications of the research project undertaken

at a later point in time. In case of any substantial modification, an amendment of the study protocol signed by the Principal 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 substantial 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.

10. Deviations from the clinical study protocol

If there is a deviation from the CIP, the deviations have to be recorded and analysed in order to prevent further deviations.

11. Disposition statement for the investigational bone graft

Access to the investigational bone graft should be controlled. The investigational bone graft should only be used in the clinical trial and in accordance with the CIP.

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

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

Estimated date of receipt: 01/2024

a) *Identification of each investigational bone graft (batch number/serial number or distinct code);* Not available yet
b) *Date of expiry if applicable;* Not available yet
c) *Date of use;* Not available yet

d) *Identity of the test person;* Not available yet

12. Legal principles

12.1 Statement of compliance:

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):

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- Medical University of Graz Guideline on Standards for Good Scientific Practice
- Applicable aspects of ISO 14155
- Austrian Act on Tissue safety (Gewebesicherheitsgesetz)

12.2 Vote of the ethics committee

The clinical trial may be started only after the competent ethics committee has issued its statement of approval.

13. 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 it 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 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 for this study will be provided a subject information sheet and a consent form describing this study and providing sufficient information for subjects 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 Independent Ethics Committee (IEC) for the study. The formal consent of a subject, using the IEC-approved consent form, must be obtained before that subject is submitted to any study procedure. Prior to subject participation in the study, informed consent will be obtained from each subject. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

Informed consent will be obtained after description and discussion of the procedures.
Standardized informed consent forms will be used additionally.

14. Adverse events

14.1 Definitions

Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users

or other persons, in the context of a clinical investigation, whether or not related to the clinical trial.

Swelling, bleeding, bruising, general allergic reaction, local allergic reaction, paresthesia, sequestrum, fracture of the jaw, loss of graft, implant loss

An **Adverse Reaction** is an AE where a causal relationship to the study devices or study procedures is assumed.

Serious Adverse Event (SAE) is defined as any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury, ii. permanent impairment of

a body structure or a body function, iii. hospitalisation or

prolongation of patient hospitalisation,

iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

A **Serious Adverse Reaction (SAR)** is a SAE where a causal relationship to the study devices or the study procedures is assumed.

14.2 Recording of adverse events

The sponsor shall fully record all of the following:

(a) any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;

(b) any serious adverse event;
(c) any new findings in relation to any event referred to in points (a) to (b).

List of adverse events as being critical to the evaluation of the results of the clinical investgation:

Loss of graft

14.5 Reporting obligations

Report by the investigator to the sponsor

The sponsor shall be informed by the investigator immediately, but not later than 3 calendar days after investigation site study personnel's awareness of the event.

Report by the sponsor to the ethics committee

Reportable events that occurred within the domestic territory (Austria) have to be reported to the concerned ethics committee by the sponsor.

14.6 Pregnancy

A pregnancy test in study subjects of childbearing potential is mandatory at screening and before radiographic and invasive clinical procedures. In case of pregnancy the study subject will be excluded from the trial.

15. Premature termination or discontinuation of the trial

In case of multiple graft losses and cases of incompatibility or symptoms of graft incompatibility premature termination and unlocking of blinded data will be performed. Further sequence patients will be provided with an alternative treatment plan and enrolled in regular follow up and maintenance programs.

15.1 Termination of the trial for a proband (drop-out)

One or several of the following circumstances may lead to the termination of the trial for a single proband (this proband shall be counted as a drop-out):

- The proband's withdrawal of his/her consent
- Intolerable adverse effects
- Violation of the study protocol
- Occurrence of an exclusion criterion

- Occurrence of a disease
- Pregnancy
- Other circumstances that would endanger the health of the proband if he/she were to continue his/her participation in the trial.

15.2 Termination of the entire trial

For the benefit of, and in the interest of the probands, the Principal Investigator is authorised to terminate the trial prematurely at any time when serious adverse effects or other unforeseeable circumstances occur.

16. Clinical Investigation Report, Publication policy, Archiving

16.1 Clinical Investigation Report

The Clinical Investigation report will be provided to the concerned regulatory authorities/ethics committee/s until one year after termination of the clinical investigation.

16.2 Publication

Data will be collected, analysed and incorporated in a manuscript for publication in a highly ranked Pubmed listed scientific journal.

16.3 Archiving

The medical records of the study participants must be kept by the hospital for at least 30 years, by outpatient clinic for at least 10 years (§ 10 Para. 1 No. 3 KAKuG, § 17 Para. 2 KAG).

17. References

1. Berglundh, T. et al. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J. Periodontol. 89, S313–S318 (2018).

2. Aghaloo, T., Misch, C., Lin, G.-H., Iacono, V. & Wang, H.-L. Bone Augmentation of the Edentulous Maxilla for Implant Placement: A Systematic Review. Int. J. Oral Maxillofac. Implants 31, s19–s30 (2017).

3. Korsch, M. et al. Pre-implantological treatment routines for alveolar ridge atrophy - An investigation among maxillofacial and oral surgeons in southern Germany. BMC Oral Health 20, 195 (2020).

4. Clark, D. & Levin, L. Dental implant management and maintenance: How to improve long-term implant success? Quintessence Int. 47, 417–23 (2016).

5. Wang, Y., Zhang, Y. & Miron, R. J. Health, Maintenance, and Recovery of Soft Tissues around Implants. Clinical Implant Dentistry and Related Research vol. 18 618–634 (2016).

6. Daubert, D. M., Weinstein, B. F., Bordin, S., Leroux, B. G. & Flemmig, T. F. Prevalence and Predictive Factors for Peri-Implant Disease and Implant Failure: A Cross-Sectional Analysis. J. Periodontol. 86, 337–347 (2015).

7. Sakkas, A., Wilde, F., Heufelder, M., Winter, K. & Schramm, A. Autogenous bone grafts in oral implantology—is it still a “gold standard”? A consecutive review of 279 patients with 456 clinical procedures. Int. J. Implant Dent. 3, (2017).

8. Whitt, J. et al. Efficacy of stem cell allograft in maxillary sinus bone regeneration: a randomized controlled clinical and blinded histomorphometric study. Int. J. Implant Dent. 6, (2020).

9. Galindo-Moreno, P. et al. Histopathological comparison of healing after maxillary sinus augmentation using xenograft mixed with autogenous bone versus allograft mixed with autogenous bone. Clin. Oral Implants Res. 29, 192–201 (2018).

10. Haugen, H. J., Lyngstadaas, S. P., Rossi, F. & Perale, G. Bone grafts: which is the ideal biomaterial? J. Clin. Periodontol. 46, 92–102 (2019).

11. Kloss, F., … V. O.-C. oral implants & 2018, undefined. Comparison of allogeneic and autogenous bone grafts for augmentation of alveolar ridge defects—A 12-month retrospective radiographic evaluation. Wiley Online Libr. 29, 1163–1175 (2018).

12. Sakkas, A., Wilde, F., Heufelder, M., Winter, K. & Schramm, A. Autogenous bone grafts in oral implantology—is it still a “gold standard”? A consecutive review of

279 patients with 456 clinical procedures. Int. J. Implant Dent. 3, 23 (2017).

13. Molenaars, R. J., Schoolmeesters, B. J. A., Viveen, J., The, B. & Eygendaal, D. There is a role for allografts in reconstructive surgery of the elbow and forearm. Knee Surgery, Sports Traumatology, Arthroscopy vol. 27 1840–1846 (2019).

14. Liang, F. et al. Alternatives to Autologous Bone Graft in Alveolar Cleft Reconstruction. J. Craniofac. Surg. 29, 584–593 (2018).

15. Alyahya, A. & Swennen, G. R. J. Bone grafting in orthognathic surgery: a systematic review. International Journal of Oral and Maxillofacial Surgery vol. 48 322– 331 (2019).

16. Rtinkey. Alveolar Ridge and Sinus Augmentation Utilizing Platelet‐Rich Plasma in Combination With Freeze‐Dried Bone Allograft: Case Series; Alveolar Ridge and Sinus Augmentation Utilizing Platelet‐Rich Plasma in Combination With Freeze‐Dried Bone Allograft: Case Series. Wiley Online Library vol. 71 https://aap.onlinelibrary.wiley.com/doi/abs/10.1902/jop.2000.71.10.1654?casa_token=FHz1_PeQqi8AAAAA:FD0OOSj61a_aUT0BE2HWrGKcgL_3BR2OALsoim0EIS1hEtk4AaMGlLpmzwTjRPTmdLrIIoLryyR067s (2000).

17. Geurs, N. C. et al. Clinical and Histologic Assessment of Lateral Alveolar Ridge Augmentation Using a Synthetic Long-Term Bioabsorbable Membrane and an Allograft. J. Periodontol. 79, 1133–1140 (2008).

18. Sterio, T., Katancik, J., … S. B.-… of P. & & 2013, undefined. A prospective, multicenter study of bovine pericardium membrane with cancellous particulate allograft for localized alveolar ridge augmentation. search.ebscohost.com.

19. Nissan, J. et al. Age-related new bone formation following the use of cancellous bone-block allografts for reconstruction of atrophic alveolar ridges. Clin. Implant Dent. Relat. Res. 20, 4–8 (2018).

20. Grassi, F. R. et al. Design Techniques to Optimize the Scaffold Performance: Freeze-dried Bone Custom-made Allografts for Maxillary Alveolar Horizontal Ridge Augmentation. Materials (Basel). 13, 1393 (2020).

21. Mühlemann, S., Lakha, T., Jung, R. E., Hämmerle, C. H. F. & Benic, G. I. Prosthetic outcomes and clinical performance of CAD-CAM monolithic zirconia versus porcelain-fused-to-metal implant crowns in the molar region: 1-year results of a RCT. Clin. Oral Implants Res. 31, 856–864 (2020).

22. Pohl, V. et al. Short dental implants (6 mm) versus long dental implants (11–15 mm) in combination with sinus floor elevation procedures: 3-year results from a multicentre. J Clin Periodontol 44, 438–445 (2017).
23. Sailer, I. et al. 10-year randomized trial (RCT) of zirconia-ceramic and metalceramic fixed dental prostheses. J. Dent. 76, 32–39 (2018).

24. Payer Vincent Arnetzl Robert Kirmeier Martin Koller Gerwin Arnetzl Norbert Jakse, M. et al. Immediate provisional restoration of single-piece zirconia implants: a pro-spective case series-results after 24 months of clinical function. Wiley Online Libr. 24, 569–575 (2012).

25. Kühl, S. et al. The influence of bone marrow aspirates and concentrates on the early volume stability of maxillary sinus grafts with deproteinized bovine bone mineral - first results of a RCT. Clin. Oral Implants Res. 25, 221–225 (2014).

26. Von Arx, T. & Buser, D. Horizontal ridge augmentation using autogenous block grafts and the guided bone regeneration technique with collagen membranes: a clinical study with 42 patients. Wiley Online Libr. 17, 359–366 (2006).

27. Razi, T., Emamverdizadeh, P., Nilavar, N. & Razi, S. Comparison of the Hounsfield Unit in CT scan with the Gray Level in cone-beam CT. J. Dent. Res. Dent. Clin. Dent. Prospects 13, 177–182 (2019).

28. Bastami, F. et al. Can gray values derived from CT and cone beam CT estimate new bone formation? An in vivo study. Oral Maxillofac. Surg. 22, 13–20 (2018).
29. Edwards, P. Questionnaires in clinical trials: Guidelines for optimal design and administration. Trials vol. 11 2 (2010).

30. McGrath, C., Comfort, M. B., Lo, E. C. M. & Luo, Y. Patient-centred outcome measures in oral surgery: Validity and sensitivity. Br. J. Oral Maxillofac. Surg. 41, 43–47 (2003).

31. Papapanou, P. N. & Susin, C. Periodontitis epidemiology: is periodontitis underrecognized, over-diagnosed, or both? Periodontology 2000 vol. 75 45–51 (2017).

32. Team, R. C. R: A language and environment for statistical computing. (2013).

33. Hu, Y. & Hu, F. Balancing Treatment Allocation over Continuous Covariates: A New Imbalance Measure for Minimization. J. Probab. Stat. 2012, 13 (2012).

18. Signatures

18.1

Sponsor or his representative

By signing this document I confirm that the trial shall be performed in consideration of ISO 14155, the Declaration of Helsinki, national laws, and the current study protocol.

[redacted]

JAKSE, NORBERT
Univ. Prof. DDr.
Name, First name

18.2

Principal 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.

[redacted]

PAYER, MICHAEL
Assoz. Prof. PD. DDr.
Name, First name