Clinical Investigation Plan (CIP)

KLINISCHER PRÜFPLAN (gemäß MPG §3)/ EN ISO 14155

CAD/CAM aided manufacturing of removable and implant-retained complete dentures – a prospective clinical pilot study

Identifying number 1

2.0 / 06.06.2018

Confidentiality Statement

The information contained in this document, especially unpublished data, is the property of the sponsor of this clinical investigation of CAD/CAM complete dentures. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Independent Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the Medical University of Vienna, except to the extent necessary to obtain informed consent from those persons to whom the interventional devices may be administered.

Device Name and Manufacturer	CERAMILL FULL DENTURE PROSTHETICS: 1. VITA VIONIC® system, VITA Zahnfabrik 2. Ceramill® FDS, Amann Girrbach 3. Baltic Denture system, Merz Dental
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1 SPONSOR, INVESTIGATOR, MONITOR AND SIGNATURES

Sponsor/or representative (OEL) (MPG §3)

Medical University of Vienna, Austria or company

_____ _____

Signature (OEL) Date

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Univ.- Ass. Dr. Lana Zupancic Cepic, University Clinic of Dentistry, Medical University of Vienna, Austria

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Signature Date

Monitor/ or Representative of CRO

_____ _____

Signature Date

Statistician

Ao.Univ.- Prof. Dr. Michael Kundi

_____ _____

Signature Date

Clinical Trials Centers: University Clinic of Dentistry Vienna

Associated Departments: Dental Laboratory of University Clinic of Dentistry Vienna

2 SYNOPSIS OF THE CLINICAL INVESTIGATION

TITLE	**CAD/CAM aided manufacturing of removable and implant-retained complete dentures– a prospective clinical pilot study**
ACRONYM	Digital complete dentures
NAME OF DEVICE	CERAMILL FULL DENTURE PROSTHETICS = material systems for each process step of CAD/CAM fabrication of complete removable dentures: 1. VITA VIONIC® system, VITA Zahnfabrik 2. Ceramill® FDS, Amann Girrbach 3. Baltic Denture system, Merz Dental
DESCRIPTION OF THE PROCEDURES	The CERAMILL FULL DENTURE PROSTHETICS systems are investigational devices intended to fabricate complete dentures in individuals suffering from edentulism. The device systems are to be used only in accordance with the approved Investigational Plan on subjects who have signed an informed consent form. Device use is limited to the approved study investigators.
OBJECTIVES	This clinical investigation aims to demonstrate the equivalence of the digital process of fabricating complete removable dental prostheses for treatment of edentulous patients to the conventional process of denture fabrication (based on clinical and patient-centered outcomes). The primary objective is to demonstrate treatment efficacy of three CAD/CAM systems for designing and fabricating complete dentures, VITA VIONIC (VITA Zahnfabrik), Ceramill Full Denture System (Amann Girrbach) and Baltic Denture System (Merz Dental) in comparison to conventional complete dentures, as measured by the evaluation of clinical parameters (i.e. fit, retention, palatal base thickness, denture quality (polish), aesthetics, phonetics, occlusion and vertical dimension) and to evaluate patient's perception of prosthodontic treatment effects and satisfaction using standardized questionnaires for assessing the satisfaction with dentures and for measuring oral health-related quality of life (OHIP 20). Secondary objective is to evaluate any differences across the three digital dentures. An additional objective is to assess the ease of use of digital complete denture systems based on chairside time, number of appointments and complications during the fabrication process.
TYPE OF THE INVESTIGATION	Prospective, randomized, single-blind

PERIOD OF ENROLMENT	**First patient** **First visit**	2018	**Last patient** **First visit**	2022	**Last patient** **Last visit**	2022
CENTER(S) / COUNTRY(IES)	1 center in 1 country. Austria					
PATIENTS / GROUPS	33 patients in 3 groups 11 patients per group Randomization ratio 1:1:1					
INCLUSION CRITERIA	Completely edentulous patients older than 18 years, with alveolar ridges Class II, III or IV according to Cawood and Howell classification, who visit the University Clinic of Dentistry Vienna requiring a new set of complete dentures (CD) for the reason of impaired aesthetics and function (for example worn teeth and denture stains) of the existing ones, and willing to participate for the duration of the study (written informed consent).					
EXCLUSION CRITERIA	Severely atrophic ridges (Class V and VI), hypertrophic tissue and maxillofacial defects.					
COMPARATIVE DEVICE	Conventional set of complete dentures fabricated using heat-curing acrylics (Promolux® C34, Merz Dental, CE 0482) and denture teeth Vitapan Excell® for anterior and Vitapan Lingoform® for posterior set-up (VITA Zahnfabrik, CE 0124)					
CONCOMITANT MEDICATION/CON-COMITANT DEVICE	**None**					
EFFICACY ENDPOINTS	Primary efficacy endpoint: OHIP 20 score after one week of wearing the CD. Secondary efficacy outcomes: fit, retention, palatal base thickness, denture quality (polish), aesthetics, phonetics, occlusion and vertical dimension one week after denture placement and patients' preferences.					
TOLERABILITY / SAFETY ENDPOINTS	Gingivitis, pain, denture pressure oedema, tongue and cheek bites					
QUALITY OF LIFE	see primary efficacy outcome					
STATISTICAL METHODOLOGY	**Null and alternative hypotheses:** **The primary H_0:** Expectancies of the OHIP 20 scores for digital as compared to conventional CDs are equal. **The primary H_1**: Expectancies of the OHIP 20 scores for digital as					

	compared to conventional CDs are not equal. **The secondary H_0:** The differences in expectancies between conventional and digital CDs are equal across the three digital dentures. **The secondary H_1**: The expectancies of the differences between conventional and digital CDs differ between the three digital dentures. **Type-I and -II errors - power.** 1st Ho: α = 0.05 (α* = 0.025), ß=0.10 (power **90%)** **2nd Ho:** α = 0.05 (α* = 0.025), ß=0.16 (power **84%)** **Statistical methodology** Statistical analysis for the cross-over trials will be done by analysis of variance with treatments as within- and sequence as between-subjects factor. Normality of residuals will be tested by Kolmogorov-Smirnov tests with Lilliefors' corrected p-values and homogeneity of variances by Levene's tests. For comparison of the three CDs, differences between each arms' scores for digital and conventional CDs will be tested by one-factor analysis of variance and Tukey's post-hoc tests. Test of normality and homogeneity of variances will be performed as above. **Sample size calculation.** In previous studies a clinically meaningful difference of OHIP-20 scores of 10 has been established. This amounts to a Cohen's d=1, because the standard deviation is also about 10. There are two statistical hypotheses that will be tested based on the data obtained. Therefore, sample size determination will first be done for the first hypothesis applying a two-sided significance level of 2.5% to account for the two tests and assuming a correlation of 0.7 between the two measurements and setting the power to 90% and then determining the power for the second hypothesis at the same alpha level. Should the power for the second test fall below 80% the sample size will be increased until 80% are reached. The sample size for each of the three independent groups under the specified assumptions was determined as n=11. For the second hypothesis a comparison between the three groups of n=11 will have a power of 84% at an effect size of f=0.66 (a clinically relevant difference for at least two pairs of digital DCs).
STUDY EXTENSION	.

3 LIST OF ABBREVATIONS

CAD/CAM computer-aided design/computer-aided manufacturing

CD complete denture

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Table 1 VISIT AND ASSESSMENT SCHEDULE

PERIODS	Name	SCREENING	TREATMENT								FOLLOW-UP	
	Duration		2 months								1 year	
VISITS	Number	1	2	3	4	5	6	7	8	9	10	11
	Name	Screening	Randomization, Clinical step 1	Clinical step 2	Clinical step 3	Clinical step 4	Clinical step 5	Clinical step 6	Clinical step 7	End of study	Follow-up	Follow-up
	Time	Days/Weeks	Day 0	Week 1 (± 3 days)	Week 2 (± 3 days)	Week 3 (± 3 days)	Week 4 (± 3 days)	Week 5 3	Week 6 3	Week 7 3	Month 8	Month 14
Informed Consent		X										
Inclusion / Exclusion Criteria		X										
Medical History		X										
Anatomical impressions, Bite registration, Face-bow			X									
Functional impression, Face-bow				X								
Determination of VDO					X							
Wax try-in						X						
Denture placement (1st set)							X					
OHIP 20		X						X		X	X	X
Clinical assessment							X	X	X	X	X	X
Placement of old dentures (wash out)								X				
Denture placement after wash-out (2nd set)									X			

5 INTRODUCTION

5.1 Background information

In the recent decades, edentulism and tooth loss in European countries show a decreasing trend [1, 2]. Nevertheless, the demand for removable and implant-retained complete dentures as prosthodontic treatment option still remains high, considering the ageing population in developed countries [3].

The era of computer-aided design/computer-aided manufacturing (CAD/CAM) technology has considerably changed the fabrication process of fixed dental prosthesis, implant abutments/prostheses and maxillofacial prostheses [4], facilitating clinicians effort and reducing laboratory time and costs [5]. Since the recent introduction of the CAD/CAM technology to fabricate complete dentures (CDs) and implant prostheses, there is an ongoing paradigm shift in the method of manufacturing CDs. The increasing number of clinical reports on the application of this technology gives support to digital concept for CDs and shows the benefits to the dental practitioner and the patient [5-12].

A review of recent literature reveals several fabrication methods for digital CDs. The definitive impressions of edentulous jaws or previous dentures are to be laser scanned to obtain data for virtual tooth arrangement (CAD) followed by computer-aided manufacturing processes (CAM)[13]. The current commercial fabricating systems can be divided into two main categories, additive (rapid prototyping; printing) or subtractive manufacturing (computer numerical control – CNC machining; milling) [4, 14, 15]. The additive technique involves rapid prototyping to form a trial denture, while the definitive denture is processed by conventional laboratory procedures [4, 13]. In contrast, the subtractive method allows a wax-free manufacturing of CDs by milling a denture base from a pre-polymerized puck of denture base resin [4, 13].

Some of the available CAD/CAM systems allow the fabrication of removable complete dentures in only two appointments [4]. Besides the shortened treatment time, there are also several other possible advantages of digital fabrication of dentures, which have been discussed in the literature, such as high accuracy of denture fit since the milling of pre-polymerized acrylic resin eliminates the shrinkage of acrylic base and the decrease in the risk of microorganism colonization of the denture base [14]. Moreover, the availability of the digital data records makes a reproduction of the denture very easy and can optionally be used for a fabrication of a radiographic or surgical template for the planning and placement of dental implants [16].

5.2 Rationale of the clinical investigation

There is little evidence about the superiority of CAD/CAM complete removable and implant-retained dental prostheses regarding clinical accuracy and predictability over the conventional manufacturing process as only a limited number of studies addressed the clinical and quality of life outcomes so far [17-20]. Thus, there is a need for a comparison of CAD/CAM complete dentures with conventional wax trial dentures.

6 OBJECTIVES OF THE CLINICAL INVESTIGATION (Hypothesis)

6.1 Primary objectives (Hypothesis)

This research aims to compare the three novel CAD/CAM systems for designing and fabricating complete dentures, VITA VIONIC (VITA Zahnfabrik), Ceramill Full Denture System (Amann Girrbach) and Baltic Denture System (Merz Dental), with conventional CDs concerning clinical and patient-based outcomes.

The hypothesis is that no differences would be found in clinical outcomes and in patient ratings or preferences between digital and conventional complete dentures.

6.2 Secondary objectives (Hypothesis)

Secondary objective is to evaluate any differences across the three digital dentures.

The hypothesis is stating the equivalence of the differences in expectancies between conventional and digital CDs across the three digital dentures.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 Population

7.1.1 Subject population

The study population is recruited from patients attending the University Clinic of Dentistry Vienna. Eleven patients per group should be included, thus representing a total of 33 patients.

7.1.2 Inclusion criteria

- completely edentulous patients older than 18 years, with alveolar ridges Class II, III or IV according to Cawood and Howell classification [21]
- existing set of old complete dentures
- informed consent of the patient

7.1.3 Exclusion criteria

- severely atrophic ridges (Class V and VI)
- hypertrophic tissue
- maxillofacial defects

7.1.4 Point of enrolment

The participation in the present study is offered every patient in need of a new set of complete dentures (CD) for the reason of impaired aesthetics and function (for example worn teeth and denture stains) of the existing ones, and willing to participate for the duration of the study (written informed consent).

7.1.5 Females of childbearing potential

Females of childbearing potential can be included in the study.

7.1.6 Duration of the clinical investigation

The estimated time for every therapy step of the investigation per patient is about 30 minutes.

7.1.7 Withdrawal and replacement of subjects

Criteria for withdrawal

Subjects may prematurely discontinue from the clinical investigation at any time. Premature discontinuation from the study is to be understood when the subject did not undergo EOS examination and / or all pivotal assessments during the clinical investigation, i.e. three complete dosage-time profiles.

Subjects must be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the clinical investigation personal

Participants may withdraw their participation from the clinical trial at any time without stating a

reason and without experiencing any disadvantages in medical care.

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF and in the subject's medical records. Should the clinical investigation be discontinued prematurely, all clinical investigation materials (complete, partially completed and empty CRFs) will be retained.

Follow-up of patients withdrawn from the clinical investigation

In case of premature discontinuation after treatment with the medical device, the investigations scheduled for the EOS visit will be performed7 days after discontinuation. The subjects will be advised that participation in these investigations is voluntary. Furthermore, they may request that from the time point of withdrawal no more data will be recorded and that all biological samples collected in the course of the clinical investigation will be destroyed.

Replacement policy

Every patient is free to decide on his/her participation in the present study or withdrawal from it after the informed consent. Any decline is documented but does not influence the further dental treatment of the patient. Patients not participating will not be considered in the sample size of the study population.

7.1.8 Premature termination of the clinical investigation

The sponsor has the right to close this clinical investigation at any time. The IEC and the competent regulatory authority must be informed.

The clinical investigation or single dose steps will be terminated prematurely in the following cases:

- If adverse event/adverse devise effect occur which are so serious that the risk-benefit ratio is not acceptable
- If the number of dropouts is so high that proper completion of the clinical investigation cannot realistically be expected.

8 METHODOLOGY

The study will enrol completely edentulous patients older than 18 years, with alveolar ridges Class II, III or IV according to Cawood and Howell classification [21], who visit the University Clinic of Dentistry Vienna requiring a new set of complete dentures (CD) for the reason of impaired aesthetics and function (for example worn teeth and denture stains) of the existing ones, and willing to participate for the duration of the study (written informed consent). The participants will be randomized into 3 groups of different digital denture systems (1= VITA VIONIC, 2= Ceramill FDS, 3= Baltic Denture) using a 1:1:1 allocation ratio to ensure a balance in sample size across groups. Within each of these three groups patients will be randomized 1:1 into one of the two sequence groups: receiving first the digital and then after a washout period of one week the conventional CD or the other way around. The fabrication type of dentures will be blinded to the patient.

The conventional set of complete dentures will be fabricated using heat-curing acrylics (Promolux® C34, Merz Dental, CE 0482) and denture teeth Vitapan Excell® for anterior and Vitapan Lingoform® for posterior set-up (VITA Zahnfabrik, CE 0124) with the 5-appointment process according to the complete denture concept of the University Clinic of Dentistry Vienna: anatomical impression (first appointment); functional impression (second appointment); determination of interocclusal relation and lip support and tooth selection (third appointment); wax try-in (fourth appointment) and denture placement (fifth appointment).

The digital CDs will be fabricated following the digital protocol of the manufacturers: the articulated jaw models obtained after functional impression and bite registration will be scanned for data acquisition (Ceramill MAP 400 Scanner, Armann Girbach) and the CAD-procedures for digital dentures will be performed using EXOCAD software. VITA VIONIC® and Ceramill® FDS workflow includes the fabrication of wax setup and try-in milled out of wax blanks (VITA VIONIC® Wax, CE 0124 respectively Ceramill® D-Wax, CE 0123) with five axes milling machine Ceramill® Motion 2. The digital wax try-in will be performed in the fourth appointment together with the conventional wax set-up. After the wax try-in Ceramill® FDS dentures are completed analog (hot polymerization process), while VITA VIONIC® system uses PMMA disc (VITA VIONIC® Base, CE 0124) for the fabrication of final denture base in CAM processing with Ceramill® Motion 2. The Baltic Denture system applies prefabricated molds including a functional setup of the dental arches ([BD]KEY Set, CE 0482) for impression-taking, transfer and bite registration.This step will be accomplished in the first appointment beside the anatomical impression with alginate (conventional path). Data are digitilized by the 3D scanner and CAD design is performed by process-intergrated CAD software [BD]Creator. After transferring the data to the CAM software of the milling machine, CNC processing of the dentures is initiated. [BD]Load is system-specific milling blank with integrated, functional dental set-up. Function and aesthetics are integrated in the blank.

A lingualized occlusal relationship with front-canine guidance is requested for all CDs.

Clinical steps for both types of prostheses will be performed by one experienced prosthodontist. The clinical outcomes will be additionally judged by another specialist with at least 5 years of clinical

experience. Complications and problems through the fabrication process will be noted. The number of the patient´s visits required for fabrication (denture insertion) will also be considered. To evaluate clinical performance of the definitive prosthesis (both fabrication types) following variables will be examined at the placement visit: fit, retention, palatal base thickness, denture quality (polish), aesthetics, phonetics, occlusion, vertical dimension. Each clinical parameter will be rated according to determined grading criteria from clinically unsatisfactory (=0) to excellent (=4) similar to a 5-point Likert scale (Kattadiyil et al.). At 1-week follow-up the condition of the tissue, i.e. presence of denture sore spots will be evaluated, and the patients will be asked to wear again the old set of dentures for 1 week (wash-out phase) to have the same initial situation before the insertion of the second set of new dentures for another 1 week.

Patient's perception of prosthodontic treatment effects and satisfaction will be investigated for each set of prosthesis using standardized questionnaire for assessing the satisfaction with dentures and questionnaire for measuring oral health-related quality of life -OHIP 20 at 1- week follow-up. Baseline assessment before the received treatment will also be performed. Furthermore, patients' preferences for one or the other CD will be determined.

8.1 Treatment duration and modification

The participation in the present study is offered every patient in need of a new set of complete dentures (CD) for the reason of impaired aesthetics and function (for example worn teeth and denture stains) of the existing ones, and willing to participate for the duration of the study (written informed consent). The participation is completed after at least eight weekly treatments, each lasting approximately 30-60 minutes. Necessary corrections to the trial dentures can prolong the duration of treatment.

8.2 Medical device

8.2.1 Medical device and its` characteristics

CERAMILL FULL DENTURE PROSTHETICS:

1. VITA VIONIC® system, VITA Zahnfabrik - includes wax and PMMA blanks for the fabrication of wax try-ins and final denture bases, special prosthetic frameworks for CAM-processing of denture teeth and a bonding solution for the adhesive fixation of ready-to-use teeth in the milled bases.

2. Ceramill® FDS, Amann Girrbach - characterized by the consistency and seamless linking of all soft and hardware components, so far unique in dental technology. In contrast to full dentures milled from acrylic, including the dentition, the denture bases fabricated using setting up wax can, if necessary, be adjusted in the dental practice following try-in.

3. Baltic Denture system, Merz Dental – consisting of ^{BD}KEY Set (impression-taking, transfer and bite registration), ^{BD}Load (complete milling blank), ^{BD}Creator (software)

8.2.1 Manufacturer (model or type number including software and accessories)

VITA Zahnfabrik has been certified according to the Medical Device Directive and the following product bears the CE mark **VITA VIONIC®** (CE 0124).

Amann Girrbach AG (CE 0123)

Merz Dental (CE 0482)

8.2.2 Installation and handling instructions

Delivery & storage conditions of the medical device

At room temperature. Store in a dry location. Protect from direct sunlight and temperatures above 25 °C.

Packaging and labeling of the medical device

Not relevant.

Accountability of medical devices

Not relevant.

8.2.3 Intended use

Digital full denture systems will be used for fabrication of complete dentures to provide functional and aesthetic treatment in edentulous patients. The maintenance therapy includes checks and aftercare at the dentist.

8.2.4 In/decrease of the treatment frequency

The number of visits till completion of the treatment may be increased, if corrections to the trial dentures are necessary.

8.2.5 Interruption of the treatment

Not intended.

8.2.6 Premature permanent discontinuation of the treatment

Premature permanent discontinuation due to an adverse event

If the reason for premature permanent discontinuation of clinical investigation is an AE, the patient should have a "Premature EOS" visit with all the assessments performed before the discontinuation of the treatment with the medical device, whenever possible.

Premature permanent discontinuation due to another reason than adverse event

If the reason for premature permanent discontinuation of clinical investigation is not an AE, the patient should be withdrawn (withdrawal of consent) and have the EOS visit with all the assessments performed before the medical device discontinuation, whenever possible.

8.2.7 Procedures for subjects compliance

The patient is monitored and instructed by a staff member of the study team. An additional examination of the patient's compliance apart from the in- and exclusion criteria is not intended.

8.2.8 Concomitant medication

Not relevant.

8.2.9 Interactions, reverse reactions and side effect of the medical device

Side effects are not known to date.

8.3 Randomization and stratification

The participants will be randomized into 3 groups of different digital denture systems (1= VITA VIONIC, 2= Ceramill FDS, 3= Baltic Denture) using a 1:1:1 allocation ratio to ensure a balance in sample size across groups. Within each of these three groups patients will be randomized 1:1 into one of the two sequence groups: receiving first the digital and then after a washout period of two weeks the conventional CD or the other way around.

8.4 Blinding

The fabrication type of dentures will be blinded to the patient. Blinding of the investigator is not feasible.

8.5 Benefit and risk assessment

The introduction of CAD/CAM technology in the field of prosthodontics has significantly changed the manufacturing methods of dentures with the aim of accelerating and facilitating everyday clinical practice. The superiority of computer-aided planning and production of complete dentures compared to the conventional procedure, however, has not yet been scientifically proven. In addition, scientific evidence is also lacking regarding clinical effectiveness of digital complete dentures. The purpose of this clinical study is to compare clinical treatment outcomes and patient satisfaction for digitally and conventionally processed CDs with the aim of finding the most proper therapy option for edentulous patients.

Problems are not expected to occur during the study. There are no injury risks or burden in study participants. The low risk is offset by a high benefit of the study.

8.6 Clinical investigation procedures

8.6.1 General rules for clinical investigation procedures

- All clinical investigation measures like blood sampling and measurements (vital parameters, ECG, etc.) have to be documented with date
- In case several clinical investigation procedures are scheduled at the same time point, there is no specific sequence that should be followed.
- The dates of all procedures should be according to the CIP. The time margins mentioned in the clinical investigation flow chart are admissible. If for any reason, a clinical investigation procedure is not performed within scheduled margins a CIP deviation should be noted, and the procedure should be performed as soon as possible or as adequate.
- If it is necessary for organizational reasons, it is admissible to perform procedures which are scheduled for one visit at two different time points. Allowed time margins should thereby not be exceeded.

8.6.2 Screening investigation

A screening investigation is not intended.

8.6.3 Treatment

The patients will undergo the 5-appointment process according to the complete denture concept of the University Clinic of Dentistry Vienna: anatomical impression (first appointment); functional impression (second appointment); determination of interocclusal relation and lip support and tooth selection (third appointment); wax try-in (fourth appointment) and denture placement (fifth appointment). If corrections needed, the wax try-in may be repeated. Both trial dentures (conventional and digital) will be tried in the same visit (fourth appointment). The first denture set (randomly assigned) will be worn for 1 week and then the patients will be instructed to change to the old dentures for 1 one week (wash-out period). Finally, the other new denture set will be applied for the period of 1 week. At the last visit the patients will receive both types of dentures and can decide which one they are going to use permanently.

8.6.4 Laboratory tests

There will be no laboratory tests.

8.6.5 End-of-clinical investigation (EOI) examination

Study participation is limited to the time of approximately 2 months needed to complete the treatment plan, which in turn defines the end of the clinical investigation. After 6 months a regular follow-up is recommended.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse event (AE)/adverse device effect (ADE)

9.1.1 Summary of known and potential risks of the medical device

No adverse events are known to date. A potential risk of allergic reactions is very low.

9.1.2 Definition of adverse event and adverse device effect

An **Adverse Event (AE)** is any adverse change from the subject's baseline condition, i.e. any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the medical device.

Adverse event include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.

- Disease or medical condition detected or diagnosed after treatment with the medical device even though it may have been present prior to the start of the clinical investigation.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the clinical investigation.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to clinical investigation-mandated procedures.
- Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the clinical investigation.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the clinical investigation lead to interruption or permanent discontinuation of medical device.

Adverse events do not include:

- Pre-planned interventions or occurrence of endpoints specified in the CIP are not considered AEs, if not defined otherwise.
- Medical or surgical procedure, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Misuse of either medical device or concomitant medication without any signs or symptoms. However, misuse must be mentioned in the Medical Device Inventory/ Treatment Log.

An **Adverse Device Effect (ADE)** is any adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

Furthermore this includes any event that is a result of a use error or intentional misuse.

9.2 Serious adverse event (SAE)/ serious adverse device effect (SADE)

A Serious Adverse Event (SAE)/Serious adverse device effect is defined as any AE/ADE fulfilling at least one of the following criteria:

- leads to a death,
- leads to a serious deterioration in the health of the subject that
    1) resulted in a life-threatening illness or injury,
    2) resulted in a permanent impairment of a body structure or a body function,
    3) required in-patient hospitalization or prolongation of existing hospitalization,
- leads to fetal distress, fetal death or a congenital abnormality or birth defect.
- is an important medical event that may not immediately result in death, be life-threatening, or require hospitalization but may be considered as SAEs/SADEs when, based upon appropriate

medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

- shows the occurrence of a malignant tumor (§3 (16) MPG).

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

9.2.1 Hospitalization – prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.

An additional overnight stay defines a prolongation of existing hospitalization.

The following is not considered an SAE/SADE and should be reported as an AE/ADE only:

- Treatment on an emergency or out subject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

9.2.2 Pregnancy

Any pregnancy that occurs during study participation must be reported to the sponsor. **To ensure subjects safety, each pregnancy must be reported to the sponsor immediately.** A pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the sponsor.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study.

9.3 Severity of adverse events/adverse device effects

The severity of clinical AEs /ADEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.

If the severity of an AE/ADE worsens during medical device administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

Mild

Event may be noticeable to subject; does not influence daily activities; the AE /ADE resolves spontaneously or may require minimal therapeutic intervention;

Moderate

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE/ADE produces no sequelae.

Severe

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE/ADE produces sequelae, which require prolonged therapeutic intervention.

A mild, moderate or severe AE/ADE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

9.4 Relationship to medical device

The investigator will assess the causal relationship between the medical device and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow known response pattern to the suspect medical device (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely

- There is a reasonable temporal relation between the AE and the medical device, but there is a plausible other explanation for the occurrence of the AE.

Possibly

- Follows a reasonable temporal sequence from administration of the medical device.
- The AE may equally be explained by the study subject's clinically state, environmental or toxic factors, or concomitant therapy administered to the study subject.
- The relationship between the medical device and AE may also be clinically plausible.

Probably

- Follows a reasonable temporal sequence from administration of the medical device, and plausible reasons point to a causal relation with the medical device.

Related

- Follows a reasonable temporal sequence form administration of the medical device.
- Follows a known response pattern to the medical device (if response pattern is previously known).
- No other reasonable cause is present.

Not assessable

- The causal relationship between the medical device and the AE cannot be judged.

9.5 Reporting procedures

A special section is designated to adverse events in the case report form. The following details must thereby be entered:

- Type of adverse event
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, resolving, not resolved, resolved with sequelae, unknown, fatal)
- Relation to medical device (Related/ Probably/ Possibly/ Unlikely/ Not related/ Not assessable)

Adverse events are to be documented in the case report form in accordance with the above mentioned criteria.

9.5.1 Reporting procedures for SAEs/SADEs

In the event of serious, the investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and made available to the clinical investigator immediately. The following details should be documented (in compliance with the requirements for safety reporting of the national regulatory authority):

- Patient number
- Study identification (Title)
- Patient: initials, date of birth, sex
- The suspected medical device
- The adverse event assessed as serious
- Short description of the event, outcome and any interventions
- Device related or non-device related

The written report is divided into two parts:

- Initial report: Informs about what has happened (AE/ADE assessed as serious), if there is a relationship to the medical device, and which action was set.
- Follow up-Report: informs about the outcome

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall:

- review the investigators assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device
- review all devices deficiencies and determine and document in writing whether they could have led to a serious adverse device effect
- report or ensure the reporting of all SAEs, whether or not related to the medical device, to the EC and regulatory authorities (AGES)!

10 FOLLOW-UP

10.1 Follow-up of clinical investigation participants including follow-up of adverse events

The first follow-up of the study participants is scheduled 6 months after data collection for the clinical investigation is completed. Further follow-ups should take place once a year.

10.2 Treatment after end of clinical investigation

A treatment after end of clinical investigation depends on the patient's demands and may include the removal of denture sore spots, remounting or relining of the denture base.

11 STATISTICAL METHODOLOGY AND ANALYSIS

11.1 Analysis sets

Efficacy analysis will be performed on the per-protocol set since the primary outcome can only be evaluated if the patient had worn the two CDs for one week (-1 day, +7 days).

Protocol violations will be reported and reasons will be included among the safety analyses. Safety analysis will be done based on both, the intention to treat as well as the per-protocol, sets.

11.2 Sample size considerations

In previous studies a clinically meaningful difference of OHIP-20 scores of 10 has been established. This amounts to a Cohen's d=1, because the standard deviation is also about 10.

There are two statistical hypotheses that will be tested based on the data obtained. The first is stating the equivalence of the expectancy of the scores for digital as compared to conventional CDs. The second is stating the equivalence of the differences in expectancies between conventional and digital CDs across the three digital dentures. Therefore, sample size determination will first be done for the first hypothesis applying a two-sided significance level of 2.5% to account for the two tests and assuming a correlation of 0.7 between the two measurements and setting the power to 90% and then determining the power for the second hypothesis at the same alpha level. Should the power for the second test fall below 80% the sample size will be increased until 80% are reached.

The sample size for each of the three independent groups under the specified assumptions was determined as n=11. For the second hypothesis a comparison between the three groups of n=11 will have a power of 84% at an effect size of f=0.66 (a clinically relevant difference for at least two pairs of digital DCs).

11.3 Relevant CIP deviations

All CIP deviations will be listed in the study report.

No deviations from the CIP and of any type will be made without complying with all IRB/EC established procedures in accordance with applicable regulations.

11.4 Statistical analysis plan

Statistical analysis for the cross-over trials will be done by analysis of variance with treatments as within- and sequence as between-subjects factor. Normality of residuals will be tested by Kolmogorov-Smirnov tests with Lilliefors' corrected p-values and homogeneity of variances by Levene's tests.

For comparison of the three CDs, differences between each arms' scores for digital and conventional CDs will be tested by one-factor analysis of variance and Tukey's post-hoc tests. Test of normality and homogeneity of variances will be performed as above.

11.5 Missing, unused and spurious data

Spurious data will be checked against the documents and corrected if necessary. Data outside the range of validity will be considered missing if the correct data cannot be revealed. No imputation for missing data will be applied.

11.6 Endpoints analysis

11.6.1 Primary endpoint analysis

The primary outcome is defined as the OHIP 20 score obtained after one week of wearing the CD. This outcome has been preferred over the clinical assessment due to the fact that the physician performing the assessment cannot be fully blinded as to the type of CD.

11.6.2 Secondary endpoint analysis

Secondary outcomes are fit, retention, palatal base thickness, denture quality (polish), aesthetics, phonetics, occlusion and vertical dimension one week after denture placement and patients' preferences.

11.6.3 Safety and tolerability endpoints

11.6.4 Baseline parameters and concomitant medications

Baseline parameters include socio-demographic data and dental clinical history as obtained by standard protocols. These data will be used for descriptive purposes and to check the efficacy of the randomization.

11.6.5 Exploratory analyses

Exploratory analyses will be performed on the secondary efficacy outcomes. These analyses will include descriptive statistics (frequency distribution, means and standard deviations, medians and interquartiles, as appropriate) and non-parametric statistical tests. For the latter, being exploratory, p-values will be considered as preliminary.

11.7 Interim analysis

No interim analyses are planned.

11.8 Software program(s)

For statistical analysis Stata 13.1 (StataCorp, Texas, USA) will be used.

12 DOCUMENTATION AND DATA MANAGEMENT

12.1 Documentation of study results

A subject screening and enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

12.1.1 Case report form (CRF)

For each subject enrolled, regardless of study drug initiation, a CRF must be completed and signed by the Investigator or a designated sub-Investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis.

If screening failures should not be documented in the CRF, this has to be clearly defined in the protocol.

CRF entries and corrections will only be performed by study site staff, authorized by the Investigator.

In a paper based CRF all forms should be completed and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator, sub-investigator or study nurse.

The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately.

The monitor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site.

12.1.2 Data collection

Data collected at all visits are entered into an interactive form. The CRFs will be source documents verified following guidelines established before study onset as detailed in the Monitoring Plan. Maintenance of the study database will be performed by the principal investigator (L. Zupancic Cepic).

12.2 Safekeeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file with all essential study documents, and subject clinical source documents.

The investigator's file will contain the CIP/amendments, Manual for Medical Device, CRFs (eCRF printout), data clarification and query forms, EC/IRB and Regulatory Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per European Standard of EN ISO 14155 and regulatory requirements.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as needed to comply with national regulations. If source documents are not durable as long as needed (e.g. ECG printouts) they must be preserved as a copy. No study document should be destroyed without prior written approval from the Department of ……

When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

12.3 Quality control and quality assurance

12.3.1 Periodic Monitoring

Not intended.

12.3.2 Audits and inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to regulatory authority inspectors. The main purpose of an audit or inspection is to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

12.4 Reporting and publication

12.4.1 Final report

Within one year after the completion of the study, a full Final Report will be written by the principal investigator.

12.4.2 Publication of study results

The findings of this study will be published by the investigators in a scientific journal and presented at scientific meetings. The manuscript will be circulated to all co-investigators before submission. Confidentiality of subjects in reports/publications will be guaranteed.

13 ETHICAL AND LEGAL ASPECTS

13.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical investigation, the patient must give written consent to participation in the study.

During the instruction the patients are to be made aware of the fact that they can with-draw their consent – without giving reasons – at any time without their further medical care being influenced in any way.

In addition to the comprehensive instructions given to the patients by the investigator, the patients also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.

The patients must agree to the possibility of study-related data being passed on to relevant authorities.

The patients must be informed in detail of their obligations in relation to the proband insurance in order not to jeopardize insurance cover.

13.2 Acknowledgement / approval of the clinical investigation

The investigator (or a designated CRO) will submit this CIP and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the clinical investigation, and should be documented in a dated letter to the investigator.

Serious Adverse Events /Serious Adverse Device Effects have to be reported to the ethics committee and to the Austrian Agency for health and Food Safety (AGES).

Adverse events / Adverse device effects- whether serious and/or unexpected, and possibly endangering the safety of the study participants are likewise to be reported to the ethics committee.

The clinical investigation shall be performed in full compliance with the valid legal regulations according to the Medical Device Law (MPG Medizinproduktegesetz as actual amended) of the Republic of Austria and the ISO 14155 (as actual amended)

The study must be notified to the Austrian Agency for Health and Food Safety (AGES) and Ethics Committee.

13.2.1 Changes in the conduct of the clinical investigation plan

Amendments of the clinical investigation plan

Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Termination of the clinical investigation

If the sponsor or the investigator decides to terminate the clinical investigation before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator, sponsor or designated CRO will notify the relevant regulatory authorities and EC. Documentation will be filed in the Trial Master (Clinical Investigation) clinical investigation and Investigator Files.

13.3 Insurance

According to the ethical committee of the Medical University of Vienna insurance is not required for the present study.

13.4 Confidentiality

The information contained in this document, especially unpublished data, is the property of the principal investigator. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the principal investigator, except to the extent necessary to obtain informed consent from those persons to whom the medical device may be treated with.

13.5 Ethics and legal requirements

13.5.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 56th WMA General Assembly, Tokyo, Japan, 2008).

13.5.2 Good Clinical Practice (according EN ISO 14155)

ISO 14155 addresses good clinical practices for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety and performance of medical devices for regulatory purposes.

It specifies general requirements intended to:

- protect the rights, safety and well-being of human subjects,
- ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other
- bodies involved in the conformity assessment of medical devices.

The investigator of the clinical investigation shall guarantee that only appropriately trained personnel will be involved in this. All clinical investigations must follow the European Standard of EN ISO 14155 and the regulatory requirements.

14 APPENDICES

e. g. Informed Consent Form (Version; Date), Manual of medical Device, IB etc.

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