A Double-Blind Randomized Controlled Trial (RCT) of Titanium-13Zirconium versus Titanium Grade IV Small-Diameter Bone Level Implants in Edentulous Mandibles – Results from a 1-Year Observation Period

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ABSTRACT

Background: The use of endosseous dental implants has become common practice for the rehabilitation of edentulous patients, and a two-implant overdenture has been recommended as the standard of care. The use of small-diameter implants may extend treatment options and reduce the necessity for bone augmentation. However, the mechanical strength of titanium is limited, so titanium alloys with greater tensile and fatigue strength may be preferable.

Purpose: This randomized, controlled, double-blind, multicenter study investigated in a split-mouth model whether small-diameter implants made from Titanium-13Zirconium alloy (TiZr, Roxolid™) perform at least as well as Titanium Grade IV implants.

Methods and Materials: Patients with an edentulous mandible received one TiZr and one Ti Grade IV small-diameter bone level implant (3.3 mm, SLActive®) in the interforaminal region. The site distribution was randomized and double-blinded. Outcome measures included change in radiological peri-implant bone level from surgery to 12 months post-insertion (primary), implant survival, success, soft tissue conditions, and safety (secondary).

Results: Of 91 treated patients, 87 were available for the 12-month follow-up. Peri-implant bone level change (-0.3 ± 0.5 mm vs -0.3 ± 0.6 mm), plaque, and sulcus bleeding indices were not significantly different between TiZr and Ti Grade IV implants. Implant survival rates were 98.9 percent and 97.8 percent, success rates were 96.6 percent and 94.4 percent, respectively. Nineteen minor and no serious adverse events were related to the study devices.

Conclusion: This study confirms that TiZr small-diameter bone level implants provide at least the same outcomes after 12 months as Ti Grade IV bone level implants. The improved mechanical properties of TiZr implants may extend implant therapy to more challenging clinical situations.

KEY WORDS: alloy, bone level implant, double-blind, edentulous mandible, Locator, RCT, Titanium, Zirconium

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INTRODUCTION

Partial or full edentulism impairs masticatory function significantly and is a major oral health concern in a large part of the adult population.[1] Traditional treatments comprising prostheses are often inadequate in restoring full masticatory function and can negatively affect nutrition, physical appearance, and self-esteem[2]. These problems generally worsen with age as additional teeth are lost and alveolar bone resorption further renders the stability of conventional dentures difficult.[3] To overcome these limitations and facilitate masticatory function, the attachment of dentures to endosseous dental implants has become common clinical practice.[1,4,5]

Demographic data indicate increasing proportions of the elderly in the population and augmented individual life expectancies. Despite a trend to lose natural teeth later in life, edentulism remains a relevant oral health condition in elderly adults.[6,7] A recent Swiss survey revealed that 37 percent of the population aged 85 years and over were edentulous.[8] Tooth loss implies significant functional and structural changes which can only partly be restored by means of conventional complete dentures. The insertion of two interforaminal implants to support and retain a lower denture has proven to be an efficient, cost-effective, and moderately invasive treatment option.[9] Implant-supported overdentures allow for a significantly better chewing efficiency and decrease the bone loss in the implant-supported areas.[10,11] In addition to these functional and structural advantages, they can improve the edentulous patient's self-confidence, well-being, and social interactions and thus contribute to a better quality of life.[12] A two-implant overdenture was therefore recommended as first choice of treatment for the edentulous mandible.[13,14]

The introduction of small-diameter (≤3.5 mm) implants has improved treatment options for challenging clinical indications such as placing implants in single-tooth gaps or edentulous ridges with limited width. The material of small-diameter implants must fulfill high demands on mechanical stability to avoid overload and implant fracture. Titanium is widely used for dental implants because of its corrosion resistance and biocompatibility superior to Titanium-Aluminium-Vanadium alloys.[15] In rats, implants from pure Titanium did not cause systemic toxicity or decrease immune activity, body weight, or the weight of any individual organ. Titanium alloys containing Zirconium show better tensile and fatigue strength than pure Titanium.[16] A Titanium-Zirconium [Titanium-13Zirconium (TiZr)] alloy (Roxolid™, Institut Straumann AG, Basel, Switzerland) with the SLActive® (Institut Straumann AG, Basel, Switzerland) surface has been developed in order to increase the fatigue strength for small-diameter implants, but with comparable osseointegration as for Titanium Grade IV implants (TI Grade IV). The biocompatibility of TiZr alloys has been shown in preclinical in vitro and in vivo models. In vitro, limb bud cells grown on TiZr showed better chondrogenic differentiation compared with cells grown on pure Titanium.[17] In rats, subcutaneously implanted TiZr alloys were surrounded by less inflammatory cells and had a lower tissue response score compared with implants from pure Titanium.[15] Zirconium as implant material also increased the amount of bone-implant contact compared with pure Titanium,[18] and recently, the quality of the osseointegration of Roxolid implants with the SLActive surface has been proven to be comparable to that of titanium in minipigs.[19]

The aim of this clinical trial was to test the hypothesis that small-diameter (3.3 mm) bone level implants made from TiZr achieve at least the same outcome in terms of peri-implant bone level change, physical stability, and safety as implants made from Ti Grade IV after 6 and 12 months follow-up in patients with edentulous mandibles restored with removable overdentures.

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MATERIALS AND METHODS

Study Sites and Patients

The study was designed as a prospective randomized, controlled, double-blind, split-mouth, non-inferiority, multicenter clinical trial conducted at eight sites in five countries (Germany, Italy, Belgium, the Netherlands, and Switzerland). Male and female patients were recruited according to the inclusion and exclusion criteria detailed in Table 1.

This clinical study was carried out in accordance with the rules of good clinical practice (according to ISO

TABLE 1 Inclusion and Exclusion Criteria for Participation in the Study

Inclusion criteria
- Voluntary informed consent
- Age ≥18 years
- Edentulous mandible at the time of surgery
- Last tooth extracted >8 weeks before date of first stage surgery
- Edentulous opposing dentition with a denture (implant-borne or conventional) or natural or restored teeth
- Adequate bone height ≥9 mm above vital structures in the intraforaminal region and sufficient bone width to allow placement of 3.3 mm implants without concurrent bone augmentation
- Commitment to participate in the study for 3 years of follow-up examinations

Exclusion criteria (systemic)
- Medical conditions requiring prolonged use of steroids
- Severe hemophilia
- Bisphosphonate medication
- History of leukocyte dysfunction and deficiencies
- History of head and neck radiation or chemotherapy
- History of renal failure
- History of uncontrolled endocrine disorders
- Physical handicaps interfering with ability to perform adequate oral hygiene
- Use of any investigational drug or device within 30 days prior to implant surgery
- Alcoholism or drug abuse
- HIV infection
- Smoking >10 cigarettes or cigar equivalents per day or chewing tobacco >10 cigarette equivalents per day
- Absence of adequate birth control in females
- Conditions or circumstances which would prevent completion of study participation or interfere with analysis of study results (eg, non-compliance)

Exclusion criteria (local)
- Local inflammation, including untreated periodontitis
- Mucosal diseases such as erosive lichen planus
- History of local irradiation therapy
- Presence of osseous lesions
- Unhealed extraction sites
- History of bone reconstruction and bone grafting techniques at site of intended implant placement
- Severe bruxing or clenching habits
- Persistent intraoral infection
- Patients with inadequate oral hygiene or unmotivated for adequate home care

Exclusion criteria (secondary)
- Need for GBR treatment at implant surgery
- Insufficient bone or any other bone abnormality that contraindicated placement
- Inappropriate treatment according to Study Protocol
- Lack of primary implant stability at time of abutment connection (ie, spinning implant at 35 Ncm torque or laterally moving implant)

14155) and approved by the Ethics Committees of all study sites. All patients provided written informed consent.

Study Design

Patients received two Straumann Bone Level Implants (Institut Straumann AG, Basel, Switzerland) of 3.3 mm diameter with the SLActive surface. One of the two implants was fabricated from TiZr alloy and the other one from Ti Grade IV. Except for the material, both devices were identical and the sterile glass-tube containers were marked A or B. Blinding keys were kept centrally at the sponsor. The first implant was randomly allocated to either the right or left interforaminal region of the edentulous mandible, the other one was placed in the contralateral side. Randomization was performed using sealed envelopes which were opened after bone exposure during surgery. Clinical examinations were performed after 6 months, but the study was unblinded only after 12 months post-surgery.

Primary outcome measure was the change of peri-implant bone level from surgery to 12 months follow-up. Secondary outcomes were soft tissue conditions (plaque index, sulcus bleeding index) after 6 and 12 months, as well as survival, success, and safety of the implants after 12 months. Calibration of the clinical examination was performed to ensure consistent evaluation of the implant sites by all investigators. After unblinding at 12 months post-surgery, follow-up visits at 24 and 36 months will be performed.

Surgical Procedure

Surgery was performed under local anesthesia following a standardized protocol. The drilling sequence was finished with a crestal drill for all implants. The implant was placed in the recipient site by means of an insertion device and a hand ratchet or motor drive. Implants of 8, 10, 12, and 14 mm length were available. Insertion depth was of bone level, but exposure of one thread was allowed if clinically adequate. Healing abutments were inserted for transmucosal healing. Sutures were removed 1–2 weeks after first-stage surgery. The healing abutments were replaced by Locator abutments (Zest Anchors LLC, Escondido, CA, USA) 6–8 weeks after surgery. The removable dentures were relined for the incorporation of the female Locator parts. No metal framework was placed.

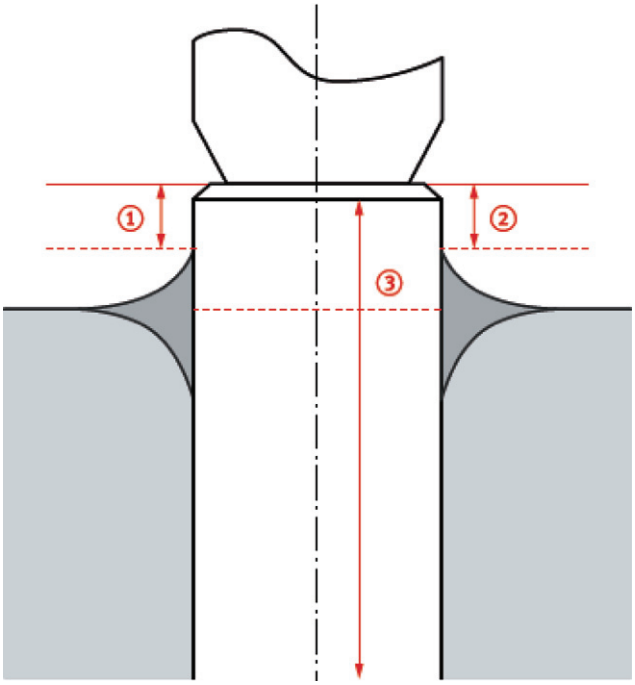

Figure 1 Schematic drawing of x-ray measurement of the implant and the surrounding bone (1 = Chamfer to first mesial implant-to-bone contact; 2 = Chamfer to first distal implant to bone contact; 3 = Length of implant).

Peri-Implant Bone Level

Standardized panoramic radiographs were taken at baseline and 12 months post-surgery, and were evaluated at the University of Bern by an independent investigator (R.P.) who was blinded to the implant material. Digital panoramic images were analyzed using NIH ImageJ 1.33 open software. Film-based panoramic images were digitized using a video camera, light box, and the image analysis program as described in Brägger (1998)[20] and Brägger (2004).[21] In both assessments, the known implant length was used as a reference to transform the linear measurements into millimeters. Reference line for bone level evaluation was the implant chamfer that is located 0.2 mm above the implant shoulder. Mesial and distal bone changes in this region were considered as remodeling. Peri-implant bone change was defined as difference in bone height with reference to the implant shoulder (below this line, the implant exhibits a SLActive surface; Figure 1).

Implant Survival and Success

Implant survival was defined as the implant being still in place at the 12-month follow-up. Implant success was defined according to Buser and colleagues[22] as

possibility for restoration and absence of: a) persistent pain, foreign body sensation and/or dysesthesia; b) recurrent peri-implant infection with suppuration; c) implant mobility; and d) continuous radiolucency around the implant.

Success criteria for the prosthesis are defined as being stable and in good function and absence of: a) abutment mobility; b) corrective measurements to the prosthesis; and c) repairs to either prosthesis or abutment.

Soft Tissue Assessment

Soft tissue status was evaluated by assessment of modified plaque index (PI) and modified sulcus bleeding index (SBI; bleeding on probing). PI and SBI at buccal, palatal distal, and mesial sites were measured on each implant according to the criteria described by Mombelli and colleagues.[23]

Safety

Safety of the implants was evaluated by recording all reported complications, adverse events (AEs), and serious adverse events (SAEs). Each AE and SAE was assessed for severity and its potential relationship to the implant device.

Statistical Analyses

Results with parametric distribution are presented as mean values (± standard deviation). Comparisons between the study groups were performed by a paired *t*-test, Wilcoxon-signed rank test, and McNemar's test as appropriate. The confirmatory non-inferiority test was performed at a one-sided 97.5 percent confidence interval (CI), whereas a difference of 0.1 mm in the change of peri-implant bone level was considered as clinically acceptable. Sample size was calculated for a significance level of 0.05 with a power of 80 percent.

The safety population comprises all randomized patients who received the test and control implant. The Intent to Treat (ITT) population comprises all randomized patients who received implants and underwent at least one efficacy assessment. The per protocol (PP) population comprises all randomized patients who received the implants without major protocol violations and whose implants reached primary stability. Primary and secondary efficacy parameters were analyzed for the ITT and the PP population. In order to avoid unnecessary re-exposition of patients to radiation, missing radiographs at the 12-months visit were substituted with radiographs at the 6-months visit if available. This might underestimate the bone loss to a minimal extent, but is a systematical bias which is ruled out by the split-mouth design and the pair-wise testing. All other missing efficacy parameters were handled as missing. Unavailable data in the safety population were treated as missing, except for severity and relationship of AEs that were regarded as severe or related to the implants, respectively.

RESULTS

Patient Sample

Patient recruitment began in October 2007 and the last 12-month follow-up was performed in September 2009. The study screened 92 patients; of these, 91 patients received implants. No efficacy data were obtained from one patient, and treatment allocation was unknown in another patient; therefore, these patients were not included in the patient set analyzed ($n = 89$, ITT population, Figure 2). Furthermore, one patient withdrew consent after implant loss, and another patient died – both before the 12-month visit.

The mean age of the ITT population was 65.8 ± 8.35 years (range 49–86 years). There were no relevant differences in the physical appearance, tissue quality, and

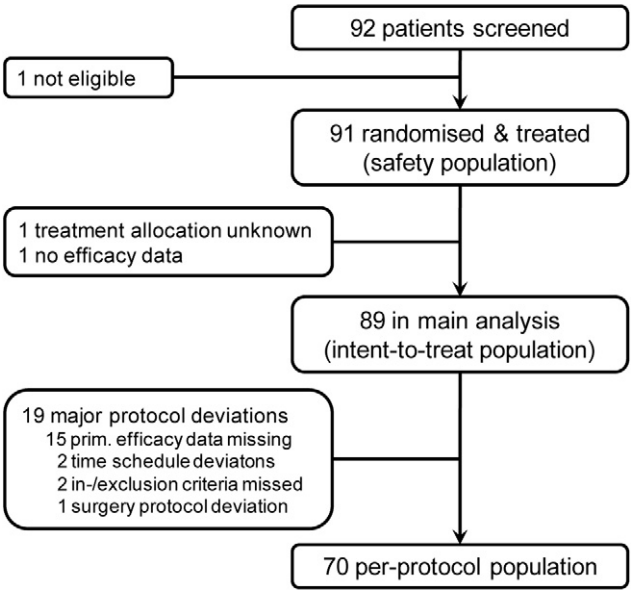

Figure 2 Patient flow. One screened patient had two major protocol violations (primary efficacy data were not assessed and surgery was not performed according to protocol) and was therefore not eligible for treatment.

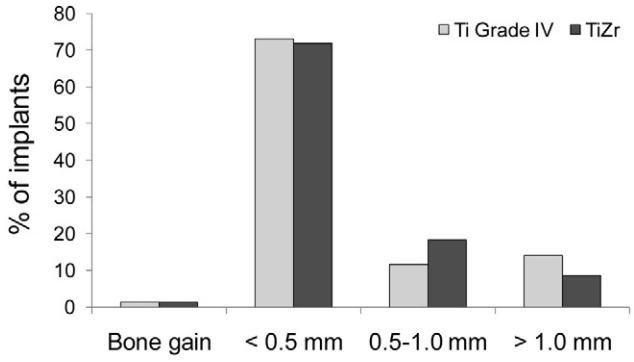

Figure 3 Peri-implant bone change at 12 months post-surgery ($n = 78$ Ti Grade IV implants, $n = 82$ TiZr implants). In the majority of implant sites, minimal change in bone level (<0.5 mm) was observed.

surface morphology of the soft tissue between the patients in the two implant groups and from time of surgery to abutment connection. Fair or poor oral hygiene was reported in 9 percent and 13.5 percent of implants in the TiZr and Ti Grade IV group, respectively.

Primary Outcome Measure

Mean peri-implant bone level change 12 months post-surgery was not significantly different between the TiZr group (−0.34 ± 0.54 mm) and the Ti Grade IV group (−0.31 ± 0.56 mm). The majority of implant sites (>70 percent in each implant group) showed minimal change in bone level (Figure 3). Of note, most of the change in bone level occurred within the first 6 months (−0.23 ± 0.35 mm vs −0.23 ± 0.40 mm). The one-sided 97.5 percent CI of the difference between the implant groups at 12-month follow-up (paired *t*-test) was [−∞, 0.087]. As the non-inferiority margin of 0.1 is not part of this confidence interval, the non-inferiority of TiZr compared with Ti Grade IV was statistically proven. The non-inferiority of TiZr was confirmed by analysis of the PP population (97.5 percent CI for treatment difference [−∞, 0.096]).

Secondary Outcome Measures

Three implants were lost during the study: one in the TiZr group and two in the Ti Grade IV group. This corresponds to survival rates of 98.9 percent (TiZr) and 97.8 percent (Ti Grade IV). All implant losses occurred before locator abutment connection. One patient presented with recurrent peri-implant infection, so that neither of his implants met the success criteria at 12 months. Considering missing data as failure, the 12-month success rates were 96.6 percent in the TiZr and 94.4 percent in the Ti Grade IV group. When excluding patients with missing data, the 12-month success rates were 98.9 percent and 98.8 percent in the TiZr and Ti Grade IV group, respectively.

Modified PI and modified SBI scores, as illustrated in Table 2, are based on the highest measures recorded at the mesial, buccal, distal, and oral sites. There was no significant difference in PI and SBI scores between the investigated implant types, neither at 6 nor at 12 months.

Safety

Out of the 91 patients of the safety population, a total of 26 patients (28.6 percent) experienced 37 AEs during the course of the study, of which 19 were judged to be related to the study device; most common were minor inflammation at the implant site, tactile implant mobility, loosening of a prosthetic component, and minor discomfort due to the surgical procedure. Seven

TABLE 2 Modified Plaque Index (PI) and Modified Sulcus Bleeding Index (SBI) according to Mombelli and Colleagues (1987)[23] at 12-Month Follow-Up ($n = 89$; ITT)

	PI		SBI	
Score	TiZr *n* (%)	Ti Grade IV *n* (%)	TiZr *n* (%)	Ti Grade IV *n* (%)
Missing	2 (2.3)	4 (4.5)	2 (2.3)	4 (4.5)
Score 0*	49 (55.1)	44 (49.4)	52 (58.4)	49 (55.1)
Score 1	14 (15.7)	12 (13.5)	22 (24.7)	23 (25.8)
Score 2	18 (20.2)	26 (29.2)	12 (13.5)	13 (14.6)
Score 3	6 (6.7)	3 (3.4)	1 (1.1)	0 (0.0)

*$p = .3617$ for PI and $p = .9933$ for SBI
TiZr, Titanium-13Zirconium.

patients (7.7 percent) experienced a SAE, none of which were related to the study device. One patient presented with an osteomyelitis related to the surgical procedure.

DISCUSSION

In patients with edentulous mandibles, small-diameter bone level implants from a TiZr alloy (Roxolid) achieved similar outcomes after 12 months as implants made from Ti Grade IV (both with SLActive surface modification). Based on the primary outcome measure of change in peri-implant bone level, TiZr was non-inferior to Ti Grade IV, and the similarity of results in the PP and ITT populations supports the robustness of the results.

Small-diameter implants are usually recommended for single-tooth gaps with limited interdental space as well as narrow edentulous ridges.[24] The increasing clinical success of these implants might reduce the necessity of invasive bone augmentation procedures, which would enhance patient acceptance of implant interventions and reduce the treatment cost. Implants with small diameters must withstand a high mechanical load to avoid implant fracture. However, the mechanical strength of pure Titanium is limited[15,16]; therefore, new materials for implant production with more favorable mechanical properties have been developed. Titanium alloys containing Zirconium show better tensile and fatigue strength than pure Titanium.[16] Furthermore, the TiZr alloy allows for the same SLA® and SLActive surface modification as Ti Grade IV. In this study, implants with the SLActive surface were used as this surface modification is associated with significantly improved bone-to-implant contact and faster healing compared with the SLA surface.[25]

In the present study, no implant fractures and no clinical differences regarding the efficacy of the TiZr alloy compared with Ti Grade IV were observed. Overall, the survival rate of both implant types in this study compared well with those of small-diameter implants in different settings.[24,26–29] A prospective evaluation of 298 two-part, 3.3 mm International Team for Implantology (ITI) Ti Grade IV implants revealed a cumulative 5-year survival rate of 98.7 percent, with two implant body fractures after 2 and 6 years, respectively.[24] In the same study, it was concluded that fatigue fracture may occur after a long period of function. In another longitudinal study comparing the clinical outcome of 122 small diameter (3.3 mm) with 208 standard diameter (4.1 mm) ITI implants over a 7-year period, cumulative survival rates for the narrow-diameter implants were 98.1 percent (maxilla) and 96.9 percent (mandible) and cumulative success rates were 96.1 percent and 92.0 percent.[28] The data presented here do not yet allow a final judgment on long-term success and implant fracture. At the 12-month follow-up, two of the 3.3 mm bone level implants (one Ti, one TiZr) in a single patient were not successful because of recurrent peri-implant infection; plaque index in this case suggests a poor oral hygiene as a possible reason.

Implants with an even smaller diameter than in the present study have been successfully used in clinical studies for the edentulous lower jaw. In a prospective study on two interforaminal two-piece mini-implants with 2.5 mm diameter in 67 edentulous patients, a 95.5 percent survival rate[30] after a mean follow-up of 6 years was found. A multicenter study on one-piece Mini-Dental-Implants (MDI 2.9 mm diameter) ($n = 1{,}029$) revealed failure rates between 6 and 31 percent in the same type of patients with four interforaminal implants.[31] This difference in success rates is not further explained in the mentioned study.

Peri-implant bone loss after 6 and 12 months was similar in both implant groups and was found to be lower than observed by Romeo and colleagues in their longitudinal study of narrow diameter implants.[28] Zarone and colleagues observed 0.6 mm bone loss 6 months after loading of narrow neck ITI implants as maxillary lateral incisor replacement.[29] In the present study, most of the bone loss occurred during the first 6 months after surgery. Similar observations were made for Astra Tech and Brånemark implants, suggesting a steady state in marginal bone levels 5 months after fixture placement.[32]

One important concern regarding the safety of implant alloys refers to their biocompatibility and the possible release of metal ions. Zirconium has similar properties to Titanium; both present neither local nor systemic toxicity. In a rat model, TiZr alloy with 50 atom percent Zirconium implanted for 8 months showed better biocompatibility than pure Titanium. It showed a lower tissue inflammatory and no sensitization response.[15] Accordingly, the soft tissue assessment showed no negative impact of the TiZr implants compared with Ti Grade IV. In the present study, no hypersensitivity reactions or other adverse events suggesting

metal ion intoxication were clinically observed in the gingival tissues.

Patient parameters are an inherent source of variability in any clinical study. The split-mouth design of the present study precludes patient-related bias, but independence of data might be compromised by cross-infection.[33] Such model has already been successfully used in implant dentistry comparing different systems.[34–37] A "carry cross effect," which is reported for periodontal trials[38] can be existent by cross infection or due to the mechanical connection of the two implants by the restoration. This potential decrease in validity is carefully weighed by the authors against the gain in precision.

CONCLUSION

This prospective randomized, controlled, double-blind clinical trial in patients with edentulous mandibles confirms the hypothesis that the TiZr alloy, Roxolid, performs at least as well as Titanium Grade IV when used as material for 3.3 mm bone level implants with SLActive surface. The improved mechanical properties of TiZr implants may extend implant therapy to more challenging clinical situations, but further clinical studies on the long-term performance of implants from this new TiZr material are required.

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