Received: 30 November 2018 | Revised: 19 February 2019 | Accepted: 22 February 2019

DOI: 10.1111/cid.12754

WILEY

ARTICLE

Safety and efficacy of a novel, gradually anodized dental implant surface: A study in Yucatan mini pigs

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Abstract

Background: A newly developed dental implant system combining advancements in surface chemistry, topography, nanostructure, color, and surface energy aims to address biological challenges and expand clinical applications.

Purpose: To assess the short- and long-term safety and efficacy of a novel, gradually anodized dental implant surface/anodized abutment.

Materials and Methods: Twenty-four Yucatan mini pigs (20-24 months old) received two dental implants in each jaw quadrant. Each site was randomized to receive either a commercially available anodized implant/machined abutment or a gradually anodized implant/anodized abutment with a protective layer. Animals were euthanized at 3, 6, and 13 weeks. Microcomputed tomography and histological analyses were performed.

Results: No significant histological differences in inflammation scores, epithelium length, bone-to-implant contact, or bone density were observed between groups for any healing time. Mucosal height was significantly higher at 3 weeks for controls (Δ = 0.2 mm); no differences were observed at 6 and 13 weeks. No significant differences in radiographic bone volume, bone-to-implant contact, trabecular thickness, and crestal bone levels were observed, irrespective of healing time. Trabecular spacing was borderline significant at 3 weeks in favor of the test implant sites; no differences were observed at 6 weeks. No significant differences were observed between experimental groups at 13 weeks.

Conclusions: The new implant system yielded results comparable to a commercially available predicate device.

KEYWORDS

biocompatible, coated materials, dental implant - abutment design, swine, miniature, osseointegration

1 | INTRODUCTION

Modern dental implant systems have achieved high survival rates due to several advances in implant design, surface technology, and prosthetic solutions.[1–4] However, expanded clinical applications have created functional and esthetic challenges that require the development of new technologies. An ideal implant system should retain all the favorable features of existing implants that have contributed to high survival rates, and introduce novel features to facilitate new clinical applications,[5,6] including better integration of the peri-implant soft tissue and a transmucosal interface that can accommodate deficiencies or changes in the peri-implant mucosa profile.[7,8] Importantly, the dental implant should retain optimized surface characteristics to achieve a prolonged shelf life.[9]

Peri-implant mucosa, the oral biofilm, and alveolar bone cells are known to be affected by surface topography.[10] Moderately rough

surfaces (surface roughness, Sa = 1-2 μm) promote osseointegration, but smooth (Sa < 0.5 μm) and minimally (Sa = 0.5-1 μm) rough surfaces facilitate cleanability.[11] Earlier dental implant designs tried to achieve the ideal balance between osseointegration and marginal bone stability by using a combination of smooth collars and rough implant body.[12,13] However, those designs created clinical and inventory challenges because implants are not always placed epi-crestally and the peri-implant mucosa characteristics greatly vary between patients.[14] With regard to esthetics, the gray color of titanium implants may become prominent if the peri-implant biotype is thin or if mucosal recession occurs.[7,15] Recent clinical studies have demonstrated that yellow/gold or pink abutments and implant collars yield better esthetic scores than regular titanium.[7,16]

Here, we evaluated a new dental implant system with combined surface chemistry, topography, nanostructure, color, and surface energy characteristics that have the potential to address several limitations of previous implant systems.[6] The new system also has a soluble protective layer to retain optimal surface characteristics during extended storage times. This study aimed to assess the short- and long-term safety and efficacy of a novel, gradually anodized dental implant surface and an anodized abutment placed into healed extraction sites, using an intraoral Yucatan mini pig model.

2 | MATERIALS AND METHODS

2.1 | Animals

This study used 24 female or castrated male Mini Yucatan swine, 20-24 months old, and a weight range of 53-82 kg, which were obtained from an approved licensed vendor (AccelLAB, Saint-Gabriel-De-Brandon, Quebec, Canada). The study was conducted at a contract research organization following good laboratory practices (AccelLAB, Saint-Gabriel-De-Brandon, Quebec, Canada). Housing, husbandry, and manipulation were performed in accordance with the Canadian Council on Animal Care and Guide for the Care and Use of Laboratory Animals regulations, and following a protocol approved by AccelLAB Institutional Animal Care and Use Committee. The animals were individually housed with ad libitum access to water and were fed a soft swine-food diet throughout the study. A soft diet was chosen to minimize mechanical trauma to the surgical site during early healing. This manuscript was prepared following the Animal Research: Reporting of in vivo Experiments (ARRIVE) guidelines.[17]

2.2 | Dental implants and abutments

NobelActive NP 3.5 × 10 mm (REF 34125) dental implant and a Multi-unit Abutment Plus Conical Connection NP 2.5 mm (REF 38881) were used for the control group (Nobel Biocare AB, Göteborg, Sweden). For the test group, NobelActive ø3.5 × 10.0 mm dental implant and a Multi-unit Abutment Plus Conical Connection NP 2.5 mm were used (Figure 1). The test dental implant system has an implant with a gradually anodized surface and an abutment with an anodized surface, as described by Milleret et al.[6] Healing Caps M-u Ti ø5.0 × 4.1 mm (REF 300162) were placed on both abutments (Nobel Biocare AB, Göteborg, Sweden).

2.3 | Sample size and treatment distribution

Based on the literature and our previous experience, we calculated that a sample size of seven animals would be sufficient to achieve 80% power in detecting the mean of paired differences of 15.0 ± 10.0% (effect size of 1.5) in osseointegration, and to achieve a significance level of 5% using a two-sided paired *t* test. In the present study, an extra animal was added to offset any losses; thus, eight animals were used for each timepoint. Four dental implants with abutments (two in each jaw quadrant) were placed per animal. Each jaw quadrant received one test and one control pair of the dental implant and abutment. Healing caps were used over all abutments.

2.4 | Presurgery procedures

The study was conducted in two phases using similar presurgery procedures for both phases. Food was restrained 12 hours prior to the procedure. The animals were preanesthetized with ketamine (25 mg/kg, IV), azaperone (4.0 mg/kg, IV), and atropine (0.04 mg/kg, IV). Animals were maintained on gas anesthesia (isoflurane/O_2 1%-3%, inhalant) and received a slow constant rate infusion of lactated Ringer's Solution (10-20 mL/kg/h, IV) to maintain hydration. The extent of anesthesia was monitored by the lack of corneal reflex, jaw tone, and swallow reflex; O_2 saturation, pulse/heart rate, and body temperature were also monitored. All general anesthetic procedures were performed and monitored by the veterinary team. Routine dental infiltration anesthesia (lidocaine HCl 2%, epinephrine 1:50 000, 5.4 mL in each jaw quadrant) was used at the surgical sites before incisions. A broad-spectrum antibiotic (ceftiofur sodium and PenPro, 300 000 IU/mL 1 mL/20 kg, IM) was administered for infection control. Animals received analgesics for pain control (buprenorphine 0.03 mg/kg, IM; buprenorphine slow release 0.05 mg/kg, SC; and carprofen 3 mg/kg, IM). Oral prophylaxis was performed via an aseptic technique using hand and ultrasonic instruments prior to both surgical phases.

2.5 | Surgical extractions

A team of experienced surgeons conducted all surgical procedures. Animals received local anesthesia, and bilateral surgical extractions of the mandibular 3rd, 4th premolar, and 1st molar teeth were performed following elevation of buccal and lingual mucoperiosteal flaps. The mandibular 2nd premolar distal cusp was adjusted if access to the adjacent premolar was limited. Approximately 5-6 mm of the alveolar bone was removed circumferentially around the teeth using a high-speed contra-angle, which was also subsequently used to section the teeth. Extractions were accomplished by using piezosurgery handpieces, elevators, and forceps. The alveolar process was flattened, and any bony spicules were contoured for enhanced flap adaptation. The periostea of the mucogingival flaps were fenestrated at the base of the flaps to allow tension-free flap apposition. The extraction sites

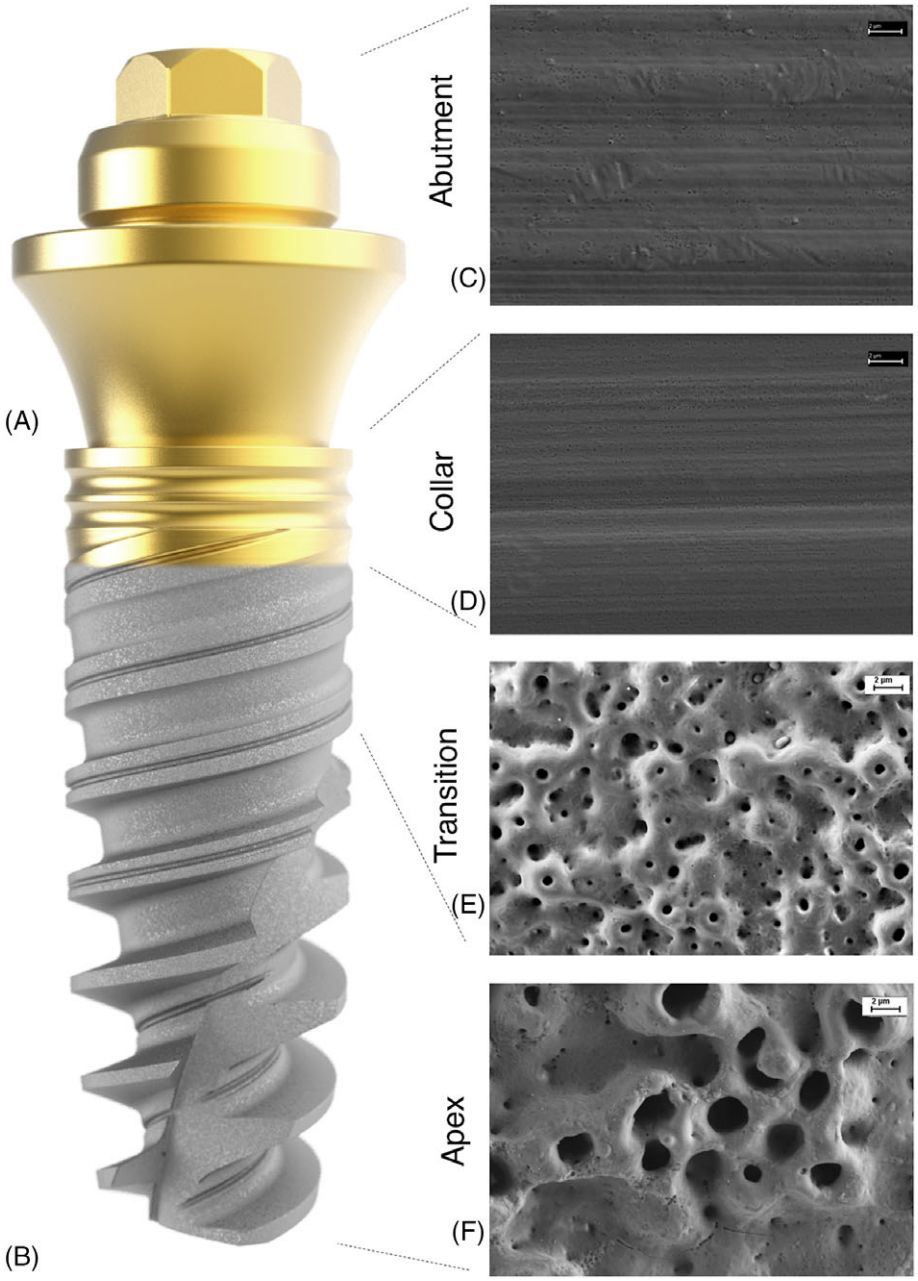

FIGURE 1 Representative images of the prosthetic abutment (A) and dental implant (B); SEM images depicting the surface of the abutment (C), implant collar (D), body (E), and apex (F)

were closed and sutured for primary intention healing and allowed to heal for 16 weeks.

2.6 | Implant placement and abutment installation

Following local anesthesia, the buccal and lingual mucoperiosteal flaps were elevated. Each animal received four dental implants and abutments, two in each jaw quadrant, according to the manufacturer's instructions. Each jaw quadrant received one test and one control dental implant and abutment. Animals were randomized to receive the test and control systems in alternate positions (anterior or posterior). The periostea of the mucogingival flaps was fenestrated at the base of the flaps to allow tension-free flap apposition. The mucogingival flaps were adapted and sutured to allow wound closure for primary intention healing. In order to avoid potential trauma from the maxillary teeth to the mandibular experimental sites, the crowns of the maxillary 1st, 2nd, and 3rd premolars were reduced in height.

2.7 | Postsurgical procedures

Routine clinical exam of extraction and implant sites was performed once daily until suture removal and weekly thereafter. Animals were sedated, and sutures were removed by experienced surgeons at approximately 14 days after surgery. Implant sites were gently cleaned during suture removal for all animals. Special care was taken to avoid any trauma to the peri-implant mucosa. Plaque control was maintained after extractions and implant placement by daily flushing

of the oral cavity with 30 mL of chlorhexidinegluconate 2% for 2 weeks and until the end of the study, respectively.

2.8 | Euthanasia

Eight animals were euthanized at 3, 6, and 13 weeks post-implant procedure using concentrated sodium pentobarbital (108 mg/kg, IV). Block biopsies including implants with abutments, bone, and soft tissue were harvested. Samples were fixed in 10% buffered formalin (pH 7.2-7.4).

2.9 | Microcomputed tomography

After fixation, each implant site was scanned using an *ex vivo* microcomputed tomography (MicroCT) scanner (Nikon Metrology X-ray and CT inspection systems: XT H 2250; Nikon Metrology Inc, Cambridge, Canada). Samples were held in place and the following settings were used: beam energy 110 Kv, 145 μA, x-ray filter copper 0.5 mm, 1.42 seconds exposure, 360 rotation, four frames per projection. For 3D reconstruction (CT Pro 3D software, Nikon Metrology, and Dragonfly software, ORS, Montreal, Canada), the gray scale was set from 25 to 75. Standard 3D morphometric parameters (CTAn software; Skyscan, Aartiesaar, Belgium) were determined in the region of interest (ROI - 250 μm surrounding the implant). Following standard operating procedures, the ROI was created subtracting the implant image from an expanded image of the implant, excluding the region above the platform and below the implant apex, leading to a ROI of the same shape of the implant. A zone corresponding to 12 μm (1 pixel) was excluded from the analysis of bone-implant contact to avoid the partial volume artifact. Representative 3D images were created using ORS Visual software (ORS, Montreal, Canada). The following parameters were evaluated for each implant:

- Bone volume/total volume (BV/TV)
- Bone-implant contact (BIC)
- Trabecular thickness
- Trabecular spacing
- Buccal and lingual crestal bone level

2.10 | Histotechnical processing

The tissue blocks remained in 10% buffered formalin for at least 3-5 days before they were prepared for light microscopy. Each implant site was processed for nondecalcified histology of the tissues surrounding the dental implants. Individual tissue blocks containing the implant and the surrounding soft and hard tissues underwent dehydration in a series of graded ethanol solutions and were finally embedded in Technovit 7200 (HeraeusKulzer, Hanau, Germany). The tissue blocks were cut in a longitudinal plane using a diamond saw. One central section was harvested from each tissue block and then reduced to a thickness of 35-55 μm using an Exakt Micro Grinding System (Oklahoma City, Oklahoma). The histologic slides were stained with Stevenel's Blue.

2.11 | Histologic analysis

One experienced masked and calibrated examiner performed the histopathologic evaluation using incandescent light microscopy (BX63, Olympus America, Melville, New York). Inflammation within the peri-implant mucosa was scored at ×20 magnification in three ROIs of 300 × 500 μm area along the abutment/mucosal interface (marginal mucosa, abutment area, and platform area). Inflammation scores were attributed to each ROI as follows:

- No inflammation (score 0): Inflammatory cells are rarely observed in the connective tissue or present in limited numbers mostly in proximity to vessels encompassing less than 10% of the ROI. Connective tissue is predominantly composed of fibroblast-like cells and fibers. No plaque, bone fragments, or foreign objects may be observed;
- Mild inflammation (score 1): Slight inflammatory infiltrate is observed within the connective tissue encompassing >10%-20% of the ROI;
- Moderate inflammation (score 2): Obvious inflammatory infiltrate is observed within the connective tissue encompassing >20%-50% of the ROI; and
- Severe inflammation (score 3): A prominent inflammatory infiltrate is observed within the connective tissue encompassing >50% of the ROI.

2.12 | Histometric analysis

Two experienced masked histologists performed the histometric evaluation using incandescent light microscopy (BX 41, Olympus America, Melville, New York) and a microscope digital camera system (Retiga 4000r, QImaging, Surrey, British Columbia, Canada) and a PC-based image analysis system (Image Pro Premier 9.2 Software, Media Cybernetics, America, Rockville, Maryland). The following recordings were performed for the buccal and lingual surfaces of the centermost sections of each implant site:

- Mucosal height: Distance between the most coronal extent of the mucosa along the abutment/healing cap and the most coronal extent of the crestal bone for buccal and lingual surfaces;
- Epithelium length: Distance between the most coronal and apical extents of the junctional epithelium along the abutment/healing cap and implant surfaces for buccal and lingual surfaces;
- Epithelium to platform distance: Distance between the most apical extent of the junctional epithelium and the implant platform for buccal and lingual surfaces;
- Crestal bone levels/loss: Distance between the most coronal extent of crestal bone along the implant and the implant platform for the buccal and lingual implant surfaces;
- First BIC: Distance between the most coronal BIC and the implant platform for the buccal and lingual implant surfaces;
- Bone density outside the implant threads (BD_{OT}): Ratio of bone to marrow spaces immediately outside the implant threads in a 500-μm wide zone within the extension of the resident bone;
- Bone density within the implant threads (BD_{WT}): Ratio of bone to marrow spaces within the root of the implant threads within the extension of the resident bone;
- BIC: bone-implant contact measured along the entire length of the implant
- Osseointegration: Percent BIC measured along the entire length of the implant within the extension of resident bone.

2.13 | Statistical analysis

For MicroCT data analysis, parametric statistics were used to describe the data and compare the experimental groups. Data collected at the implant level were aggregated at the animal level, and the animal was used as the unit of analysis. Equal variance and normality tests were performed, and the paired *t* test was used for comparisons between experimental groups. Means and standard deviations were reported in Table 1. For histometric data, nonparametric statistics were used to describe the data and compare the experimental groups. Site-level data were aggregated at the animal level, and separate analyses were carried out for buccal and lingual sites. Medians and interquartiles were reported in Tables 2 and 3, and box plots were used to illustrate the overall distribution of the data. The Wilcoxon matched-pairs signed-ranks test was used to compare experimental groups. Stata/MP 15.1 for Mac (College Station, Texas: StataCorp LP) was used for the analysis. The level of significance was set at 5%.

Examiner reliability for the histometric evaluations were assessed using repeated measurements at least 1 week apart to estimate the concordance correlation coefficient (CCC) for continuous data and Kappa statistics for categorical data. CCC was >0.91 and Kappa was >0.90 indicating a high degree of agreement.

3 | RESULTS

Ninety-six implants were placed in 24 animals with four implants per animal. One implant was lost for the control group at 6 weeks follow-up. No differences in the clinical handling of the control and test dental implants were observed. From a clinical standpoint, the test implants demonstrated better wettability than control implants, as seen by blood wicking up the implant threads during implant insertion (Figure 2). Healing was uneventful for both experimental groups.

3.1 | MicroCT observations

No statistically significant differences in mean BV/TV, BIC, trabecular thickness, and buccal/lingual crestal bone levels were observed between groups at 3, 6, or 13 weeks postsurgery (Table 1). Trabecular spacing was borderline significant at 3 weeks in favor of the test implant sites. Figure 3 shows representative reconstructed images for each experimental group at 3, 6, and 13 weeks postsurgery.

3.2 | Histologic observations and histometric analysis

Figure 4 presents photomicrographs showing a representative specimen from each experimental group at 3, 6, and 13 weeks postsurgery.

3.2.1 | Peri-implant mucosa

The histometric results for the peri-implant mucosal measurements are shown in Table 2 and Figure 5. Overall (buccal and lingual sites combined), a small but statistically significant difference in mucosal height (control = 3.5 mm vs test = 3.3 mm, $P = 0.01$) was observed at 3 weeks (Figure 5); no significant differences in mucosal height were observed at 6 (control = 3.6 mm vs test = 3.6 mm, $P = 0.67$) and 13 weeks (control = 3.1 mm vs test = 3.1 mm, $P = 0.89$). Epithelium length was 3.5 versus 2.9 mm, 3.3 versus 3.2 mm, and 3.9 versus 4.3 mm for control and test groups at 3, 6, and 13 weeks postsurgery, respectively. The epithelium reached the implant platform more frequently in the control than the test group at 3 and 6 weeks, and it was slightly below the platform at 13 weeks for both groups. No statistically significant differences were observed between control and test groups for all parameters when buccal and lingual sites were evaluated separately (Table 2).

Overall, no statistically significant differences were observed in the inflammation scores between experimental groups, irrespective of the area of interest or healing period (Figure 5). Very limited inflammation was observed at the platform level for both experimental groups (Table 2).

3.2.2 | Peri-implant bone

The histometric results for the peri-implant bone measurements are presented in Table 3 (buccal and lingual sites separate) and Figure 6 (buccal and lingual sites combined). Overall (buccal and lingual sites combined), no statistically significant differences were observed between control and test groups for all parameters evaluated at 3 and 6 weeks (Figure 6). Crestal bone levels were 0.6-0.8 mm, 0.5-0.8 mm, and 0.4-0.6 mm below the implant platform at 3, 6, and 13 weeks, respectively; no significant differences between groups were observed

TABLE 1 MicroCT morphometric recordings of the peri-implant bone according to experimental group (n = 24)

	3 weeks (n = 8)			6 weeks (n = 8)			13 weeks (n = 8)		
	Control	Test	p-value	Control	Test	p-value	Control	Test	p-value
BV/TV (%)	34.2 ± 4.0	37.3 ± 6.1	0.27	45.7 ± 8.2	47.2 ± 5.7	0.61	55.6 ± 7.9	56.5 ± 8.2	0.68
BIC (mm^2)	80.46 ± 9.86	84.16 ± 11.37	0.15	104.40 ± 18.15	97.14 ± 13.49	0.40	106.04 ± 16.02	102.29 ± 13.21	0.42
Trabecular thickness (mm)	0.145 ± 0.009	0.146 ± 0.009	0.81	0.155 ± 0.004	0.157 ± 0.004	0.43	0.168 ± 0.006	0.170 ± 0.005	0.11
Trabecular spacing (mm)	0.187 ± 0.004	0.180 ± 0.005	0.05	0.182 ± 0.014	0.175 ± 0.014	0.14	0.172 ± 0.016	0.170 ± 0.013	0.74
Crestal bone levels (mm)									
Buccal	1.371 ± 0.355	1.174 ± 0.584	0.43	1.623 ± 0.769	1.289 ± 0.612	0.25	1.433 ± 0.898	1.360 ± 0.662	0.84
Lingual	1.427 ± 0.371	1.332 ± 0.812	0.77	1.327 ± 0.603	1.478 ± 1.422	0.74	1.289 ± 0.573	1.391 ± 0.562	0.68

Abbreviations: BV/TV, bone volume/total volume; BIC, bone-implant contact.
Data are expressed as mean ± SD.

TABLE 2 Histometric recordings of the peri-implant mucosa according to experimental group (n = 24)

	3 weeks (n = 8)							6 weeks (n = 8)							13 weeks (n = 8)						
	Control			Test				Control			Test				Control			Test			
	Median	25%	75%	Median	25%	75%	p-value	Median	25%	75%	Median	25%	75%	p-value	Median	25%	75%	Median	25%	75%	p-value
Buccal																					
Mucosal height	4.2	3.9	4.7	4.1	3.4	4.7	0.07	4.1	3.7	4.5	4.5	4.1	4.8	0.26	3.6	3.3	4.2	3.6	3.3	4.0	1.00
Epithelium length	3.7	3.1	4.3	3.3	3.0	3.9	0.26	4.2	3.4	4.9	4.3	3.6	4.6	1.00	4.7	4.1	5.6	4.6	4.1	5.7	0.78
Epithelium-platform[a]	0.1	−0.3	0.8	0.5	0.2	0.8	0.21	0.2	0.02	0.6	0.1	−0.1	0.6	0.89	−0.5	−1.2	−0.1	−0.6	−1.0	−0.0	0.48
Inflammation score																					
Marginal	1.0	0.5	1.0	0.75	0.25	1.25	1.00	0.5	0.25	1.0	1.5	0.75	1.5	0.14	2	1.25	2	2	1.75	2.5	0.51
Abutment	1.0	0.75	1.25	1.0	0.75	1.25	0.82	0.25	0.0	1.5	0.75	0.0	1.0	0.88	1	0.75	1	1	0.5	1.25	0.88
Platform	1.0	0.25	1.0	0.5	0.0	1.0	0.36	0.0	0.0	0.5	0.0	0.0	0.0	0.29	1	0	1	0	0	0.75	0.36
Lingual																					
Mucosal height	2.8	2.7	3.3	2.7	2.6	2.8	0.06	3.2	3.1	3.5	2.8	2.6	3.2	0.12	2.7	2.1	3.1	2.8	2.3	3.1	1.00
Epithelium length	3.5	2.6	3.9	2.6	2.2	3.1	0.16	2.8	2.4	3.1	2.0	1.4	2.8	0.12	3.0	2.7	3.4	3.3	2.1	3.9	0.89
Epithelium-platform[a]	0.1	−0.7	0.3	0.5	−0.2	0.8	0.21	0.2	−0.4	0.9	0.9	0.6	1.1	0.12	−0.4	−0.5	0.1	−0.5	−1.2	0.3	0.78
Inflammation score																					
Marginal	1.0	0.5	1.5	1.5	1.25	2.0	0.06	1.25	1.0	1.75	1.0	0.5	1.5	0.62	2	1.5	2.25	1.5	1	1.75	0.13
Abutment	1.0	0.25	1.0	0.5	0.0	0.5	0.28	0.0	0.0	1.0	0.5	0.25	1.0	0.52	0	0	0.5	0	0	0.75	1.00
Platform	0.0	0.0	1.0	0.0	0.0	0.0	0.08	0.0	0.0	0.75	0.0	0.0	0.0	0.25	0	0	0.25	0	0	0.25	0.92

[a]Negative values indicate epithelium extension below the implant platform. Mucosal height, epithelium length, and epithelium to platform values are expressed in mm.

TABLE 3 Histometric recordings of the peri-implant bone according to experimental group (n = 24)

	3 weeks (n = 8)							6 weeks (n = 8)							13 weeks (n = 8)						
	Control			Test				Control			Test				Control			Test			
	Median	25%	75%	Median	25%	75%	p-value	Median	25%	75%	Median	25%	75%	p-value	Median	25%	75%	Median	25%	75%	p-value
Buccal																					
Crestal bone level[a]	1.1	0.8	1.2	0.8	0.6	1.2	0.57	0.7	0.4	1.3	0.6	0.5	1.1	0.94	0.4	0.2	0.7	0.2	−0.1	0.5	0.26
First BIC[a]	1.3	1.1	1.6	1.2	0.8	1.7	0.26	1.7	0.5	2.2	1.5	1.1	1.9	0.78	1.2	0.6	1.6	1.6	1.2	1.9	0.33
BIC (%)	60.1	50.1	64.4	64.3	54.6	72.6	0.16	65.3	56.0	73.9	61.0	46.8	70.1	0.40	64.9	52.2	75.2	61.3	48.0	66.0	0.67
BD_{WT} (%)	33.1	28.9	37.8	41.1	35.7	45.4	0.07	44.3	41.1	51.1	39.9	36.5	48.1	0.33	50.1	48.3	53.7	54.1	51.2	59.6	0.07
BD_{OT} (%)	45.3	42.3	48.9	52.3	44.0	58.9	0.05	55.8	53.5	61.0	53.4	49.6	58.2	0.57	58.6	54.9	69.7	71.6	63.8	73.6	0.16
Lingual																					
Crestal bone level[a]	5.3	0.3	0.8	0.4	0.2	0.6	0.09	1.0	0.5	1.1	0.4	0.3	0.7	0.33	0.8	0.4	1.0	0.6	−0.1	0.9	0.12
First BIC[a]	1.2	1.0	1.6	1.0	0.8	1.9	0.89	1.6	0.8	2.0	1.2	1.1	1.6	0.89	1.0	0.9	1.8	1.8	1.4	2.0	0.21
BIC (%)	63.2	56.6	67.6	63.7	54.2	69.7	0.67	69.0	62.6	75.2	60.8	52.6	65.9	0.16	70.8	53.8	78.0	58.5	46.3	65.1	0.05
BD_{WT} (%)	39.6	35.6	43.2	39.0	36.8	46.5	0.89	46.3	36.1	55.0	48.4	41.2	53.7	0.89	54.0	45.0	57.4	52.0	43.0	62.1	1.00
BD_{OT} (%)	51.6	48.3	59.8	50.4	45.9	54.8	0.57	49.3	44.2	57.1	49.9	48.0	54.2	0.21	59.1	44.7	66.2	62.4	53.9	68.2	0.26

Abbreviations: BD_{OT}, bone density outside the implant threads; BD_{WT}, bone density within the implant thread; BIC, bone-implant contact.
[a]Positive values indicate bone levels below the implant platform.

at 3 and 6 weeks, whereas a borderline significant difference was observed at 13 weeks favoring the test group (P = 0.049). The implant platform to first BIC distance was 1.2-1.3 mm, 1.4-1.6 mm, and 1.1-1.7 mm below the implant platform at 3, 6, and 13 weeks, respectively. Comparable osseointegration was observed between the two groups—60%-65% at 3 weeks and 59%-67% at 6 and 13 weeks. Slight increases in BD_{WT} and BD_{OT} were observed over time, with a borderline significant difference between groups at 13 weeks, favoring the test group. No other significant difference was observed for BD_{WT} and BD_{OT}. No statistically significant differences were observed between control and test groups for all parameters when buccal and lingual sites were evaluated separately, with the exception of BD_{OT} on buccal sites at 3 weeks and BIC on lingual sites at 13 weeks, which were borderline significantly higher favoring the test and control groups, respectively (Table 3).

4 | DISCUSSION

The aim of this study was to assess the short- and long-term safety and efficacy of a novel dental implant system consisting of an implant with a gradually anodized surface and an abutment with an anodized surface, both of which were shielded from atmospheric contaminants during storage via a protective layer. An intraoral mini pig model was used to compare this implant system to a commercially available implant system that consisted of a dental implant with a homogenously anodized surface and a machined abutment. At 3 weeks, the mucosa height was statistically higher in the control group compared with the test group, but this difference was minor and not observed at 6 weeks. BD_{OT} was borderline significantly higher in the test than the control group at the buccal sites, and the trabecular spacing was borderline significant in favor of the tested implant. No other significant differences in histological and radiographic parameters were observed between the control and test groups. No significant differences were observed between experimental groups at 13 weeks, excepting for a borderline significant difference for BIC on lingual sites favoring controls. Collectively, these findings support the safety and efficacy of the new implant system.

Historically, implant designs have been modified to accommodate differences in bone quality and density for better implant placement and primary stability.[4] Moderately rough surfaces, which are mostly homogeneous from collar to apex, have been developed to enhance BIC.[1,11,18] The novel implant surface tested in this study is gradually anodized, and has a surface roughness that increases from collar to apex.[6] Moderately rough surfaces, which are present at the transition and apex regions of the implant, have been shown to achieve high levels of osseointegration.[1,11] Importantly, BIC shown by the new surface was comparable to that of the predicate surface that has an estimated 10-year survival rate of 95%.[1,19] The new implant surface is ultra-hydrophilic and also presents nanostructures. Although the effects of hydrophilicity and nanoscale characteristics on clinical outcomes remain unclear, in vitro and in vivo studies have shown their potential to enhance BIC.[20,21]

Peri-implant soft tissue deficiencies and bone recession are frequent postsurgical occurrences possibly due to several contributing

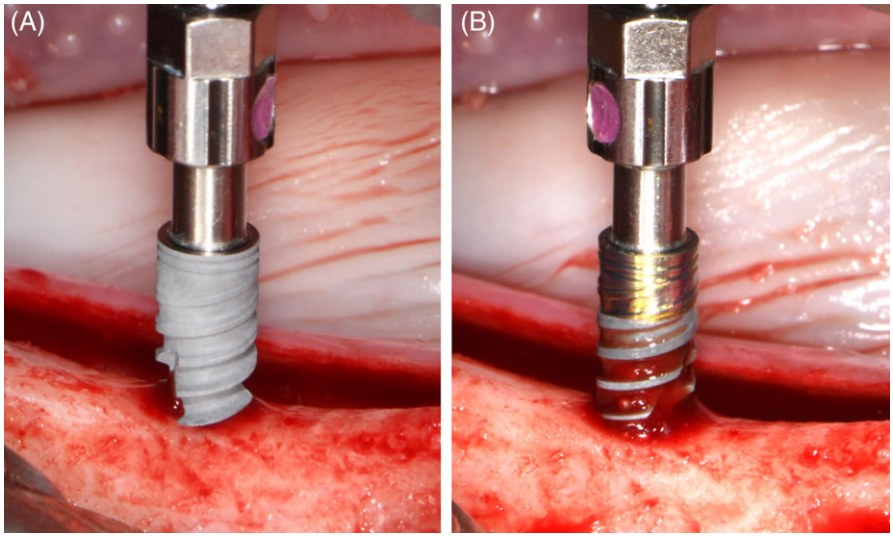

FIGURE 2 Representative pictures showing the wettability of (A) control and (B) test groups

factors including presurgical soft and hard tissue biotype, surgical trauma, implant/abutment design, time of implant placement, provisionalization, and restoration.[8,22] These deficiencies pose clinical challenges that are hard to overcome because soft and hard tissue augmentations are technique sensitive.[8,23,24] Electrochemical anodization allows manipulation of the oxide layer and nanostructure, leading

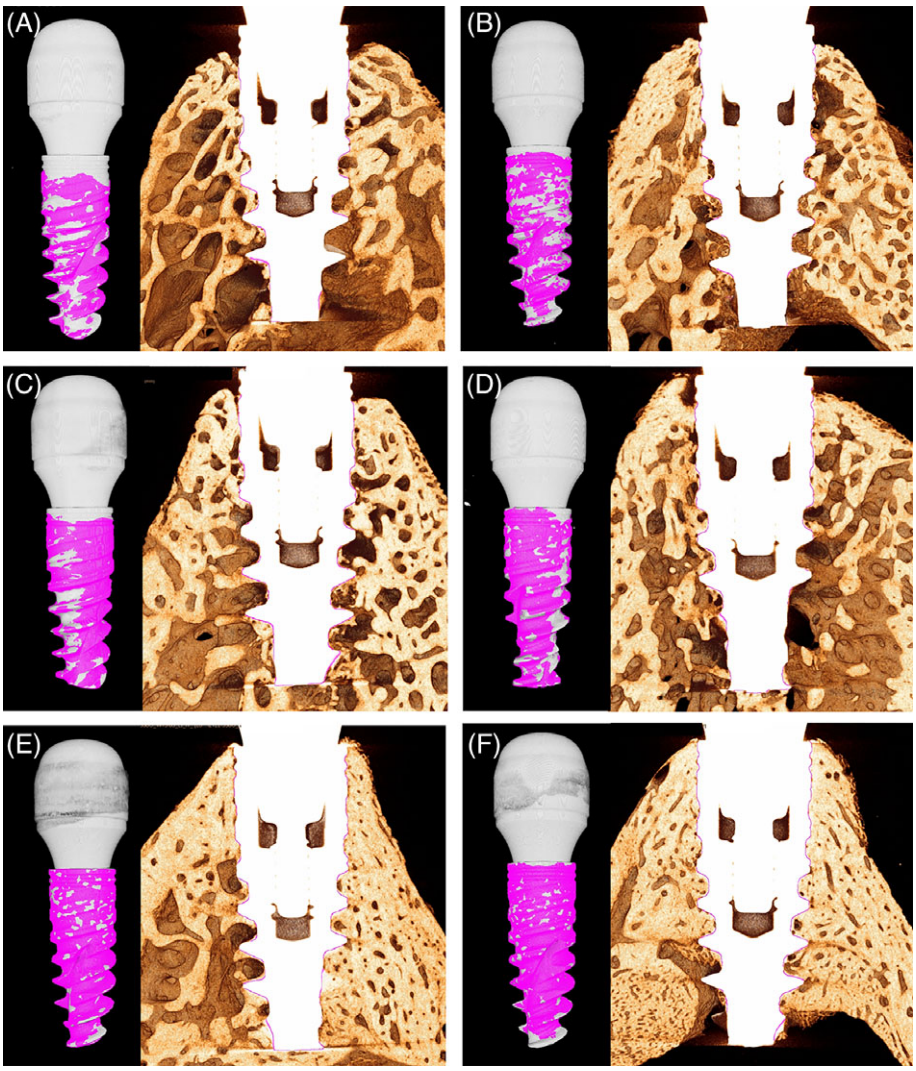

FIGURE 3 MicroCT reconstruction of representative samples from each group and healing time. A, control group, 3 weeks; B, test group, 3 weeks; C, control group, 6 weeks; D, test group, 6 weeks; E, control group, 13 weeks; F, test group, 13 weeks

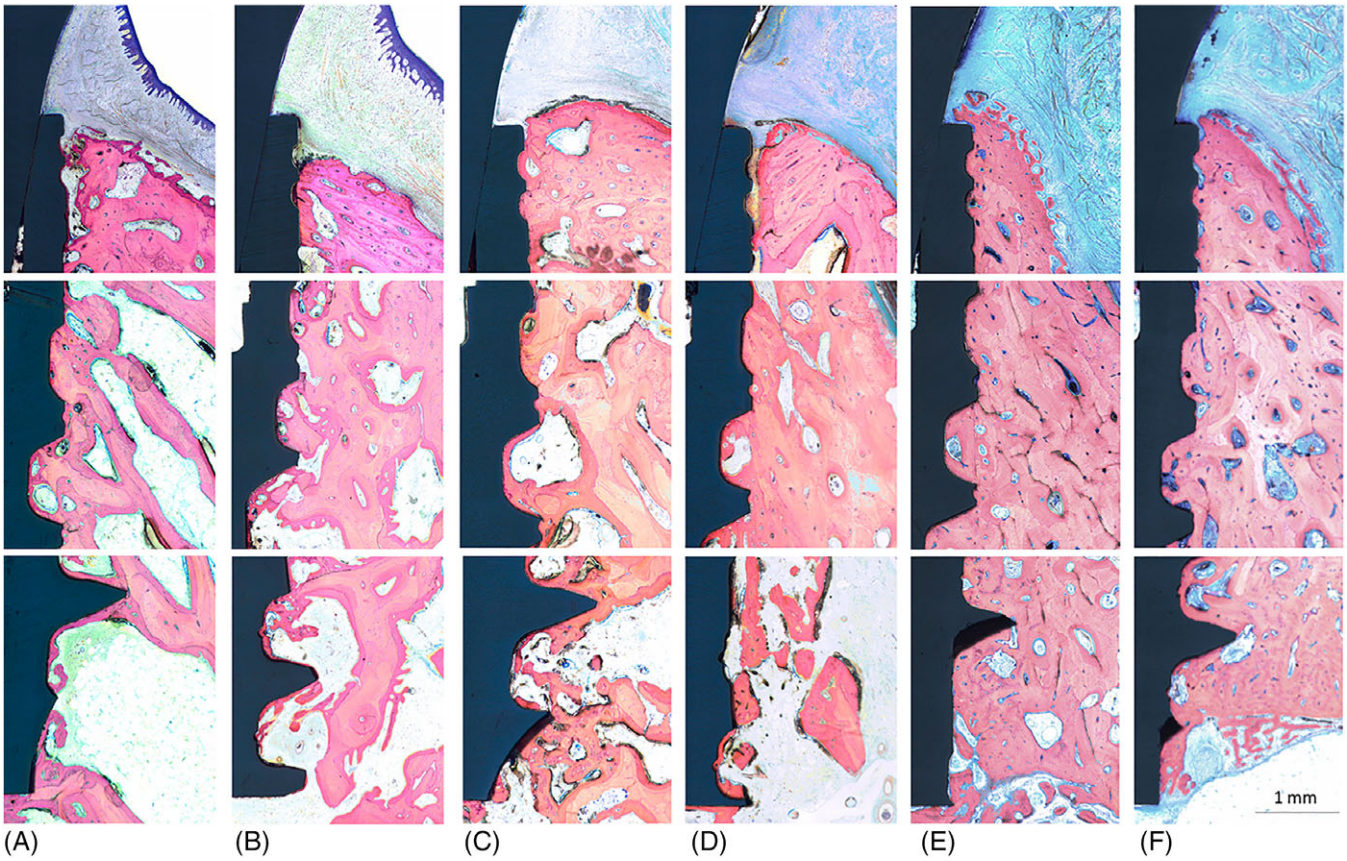

FIGURE 4 Photomicrograph (4× magnification) showing a representative specimen from each group at 3, 6, and 13 weeks. A, Control group, 3 weeks; B, test group, 3 weeks; C, control group, 6 weeks; D, test group, 6 weeks; E, control group, 13 weeks; F, test group, 13 weeks

to changes in color.[25] Although the present study did not directly address esthetics, yellow/gold or pink anodized abutments and implant collars have been shown to have better esthetic scores than regular titanium material.[7,16] Mucosal height was significantly higher in controls than experimental abutments at 3 weeks, but the no differences were observed at 6 and 13 weeks. The limited magnitude and transient nature of the difference may question its clinical relevance.

Surface roughness of several restorative materials, including crowns and abutments, is well known to correlate with increased accumulation and complexity of oral biofilms.[10,26,27] Although roughness likely has a negative effect on peri-implant inflammation, the supporting scientific evidence is currently limited with few available human studies.[28] The abutment surface modified by electrochemical anodization did not show increased surface roughness compared with the machined abutment (Sa = 0.1).[6] Moreover, in vitro evidence suggests that anodized surfaces have an antimicrobial effect.[29,30] This study showed comparable inflammatory scores for the anodized and machined abutments. Our findings are partially supported by observations of a companion clinical study.[31]

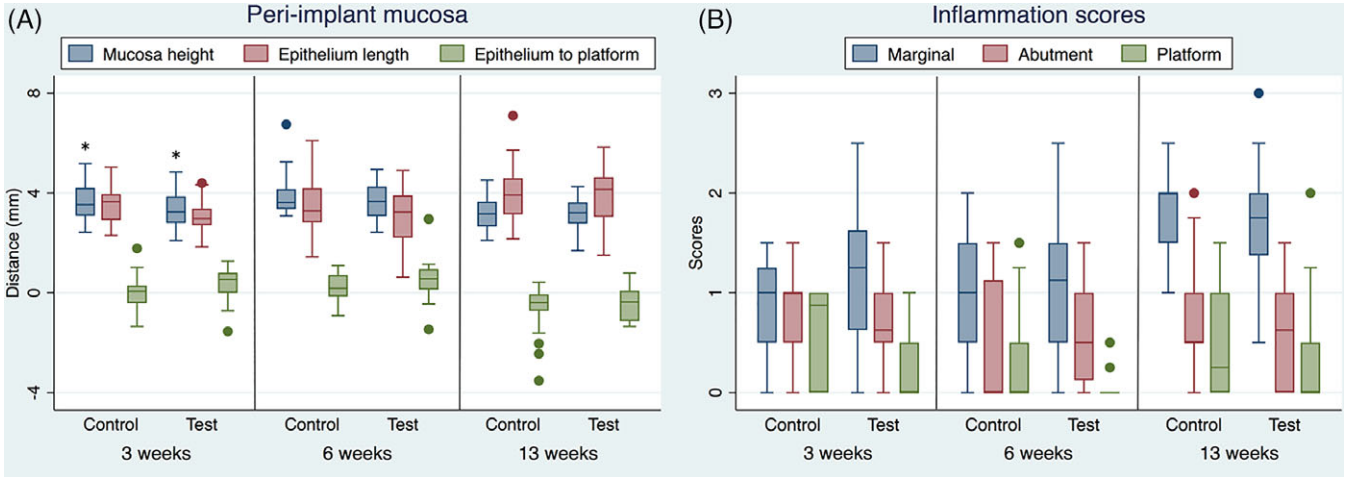

FIGURE 5 Box plot depicting peri-implant mucosal parameters: A, mucosa height, epithelium length, and epithelium to implant platform distance according to experimental group; B, inflammation scores.*Statistically significant difference ($P < 0.05$)

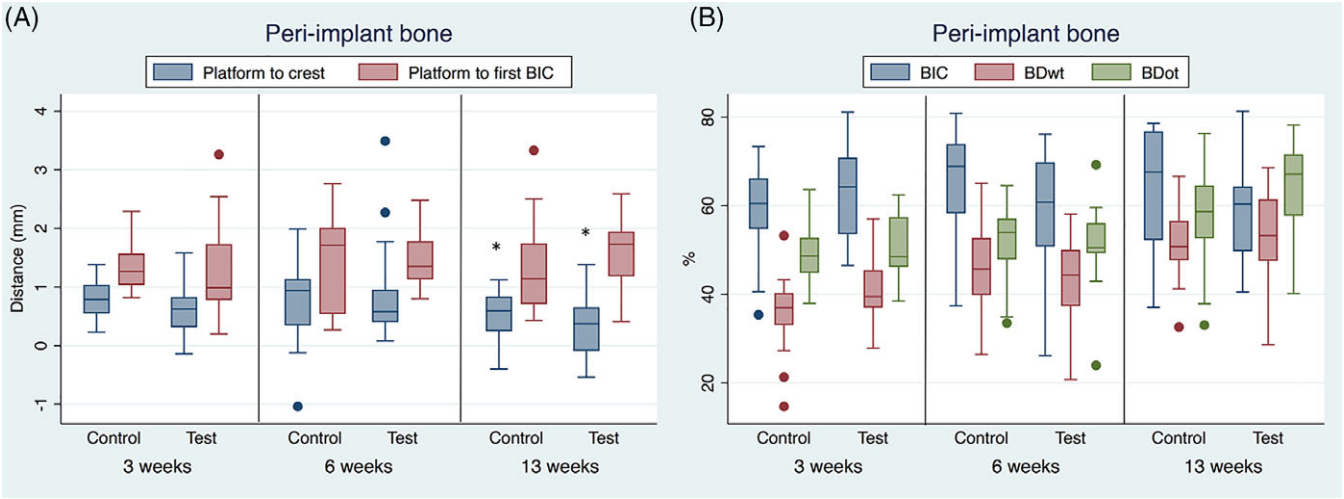

FIGURE 6 Box plot depicting peri-implant bone parameters: A, crestal bone levels and first bone-implant contact (BIC) distance; and B, BIC, bone density within the implant threads (BD_{WT}), and bone density outside the implant threads (BD_{OT}) according to experimental group. *Statistically significant difference ($P < 0.05$)

Compared with machined surface implants, moderately rough implant surfaces have shown increased BIC[20] and long-term survival.[1] However, moderately rough surface implants show greater initial marginal bone loss than machined surface implants.[1,12] The crestal bone level and first BIC distance in the minimally rough implant collar[6] are comparable to those of the benchmark implant, which has been shown to have stable radiographic marginal bone levels in clinical studies.[32,33] In this study, no significant differences in BIC were observed between the gradually anodized and standard anodized surfaces in the microCT analysis for all healing periods. In the histometric analysis, no differences in BIC were observed between groups at 3 and 6 weeks, but a borderline significant difference was observed on lingual sites favoring controls at 13 weeks; no significant differences between groups were observed at any healing period when buccal and lingual sites were combined. Collectively, these findings indicate that the minimally rough surface at the collar had no effect on the overall extent of osseointegration. Compared to controls, the BD_{OT} at buccal sites was significantly higher and trabecular spacing was significantly lower in gradually anodized surface at 3 weeks; however, no significant differences were observed at 6 and 13 weeks. The importance of these findings is unclear since the effect sizes observed were small and limited to 3 weeks.

Hydrocarbons and other atmospheric elements get deposited on the implant surface during storage under ambient conditions.[9] Studies have shown that hydrocarbons negatively affect protein adhesion,[34–36] osteoblast function,[34,35]osseointegration, and biomechanical strength in vivo.[34] In the new implant system, a protective layer has been applied during manufacturing in order to reduce surface contamination. Milleret et al[6] have shown that this strategy significantly decreases the amount of carbon content on the implant surface and maintains its hydrophilicity.[6] Importantly, the protective layer dissolves after contact with body fluids.[6] This strategy offers an attractive alternative to the use of containers filled with liquids or specific gases for storage of implant systems.[9]

Mini pigs have been extensively used in biomedical research and their use in dental implant research is growing.[37] These animals are anatomically and physiologically similar to humans,[38,39] and also show similar bone biology. Because radiographic recordings provide data on mesial/distal sites and histological sections depict buccal/lingual sites, both of which have different healing patterns, direct comparisons cannot be made between our results and actual clinical outcomes.

5 | CONCLUSIONS

The safety and efficacy of the novel dental implant system was demonstrated. The new system yielded comparable results to a commercially available predicate device. Clinical studies are necessary to confirm these findings.

ACKNOWLEDGMENTS

The authors would like to thank Dr Rodrigo Carlos Nahas de Castro Pinto for his support in the surgical procedures. Authors would also like to thank Philipp S. Lienemann and Waldemar Hoffmann (Nobel Biocare AG) for their support during the study execution.

CONFLICT OF INTEREST

This study was supported by a research grant from Nobel Biocare AG, Kloten, Switzerland. CS serves as scientific advisor and lecturer for Nobel Biocare. MSR, TF, and UDR serve as consultants for Nobel Biocare.

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How to cite this article: Susin C, Finger Stadler A, Musskopf ML, de Sousa Rabelo M, Ramos UD, Fiorini T. Safety and efficacy of a novel, gradually anodized dental implant surface: A study in Yucatan mini pigs. *Clin Implant Dent Relat Res*. 2019;1–11. https://doi.org/10.1111/cid.12754