The MIS Quality System complies with the following international quality standards: ISO 13485:2003 - Quality Management System for Medical Devices, ISO 9001:2008 – Quality Management System and Medical Device Directive 93/42/EEC. Please note that not all products are registered or available in every country or region.
Dear Readers,

MIS has made innovation one of its top priorities and key goals. Keeping up with market demands means that our innovation comes from a real need to constantly improve, advance and provide the right solution and a genuine biological advantage for the doctors and patients who may benefit from it, all the while keeping this solution as simple as possible. B+ is the latest innovation from MIS which perfectly answers the need for both simplicity and a substantial biological advantage.

Yours,

Doron Peretz
Senior V.P. Marketing & Products Development
Index.

Scientific Support

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B+ Surface. Introduction and Overview

B+ is a biological feature of MIS implants, which results in effective early and long-term osseointegration. It is comprised of a mono-molecular layer of multi phosphonates, which is permanently bound to the surface of the implant and is perceived as bone-like by the body.

Molecules of B+ chemically bind to the implant, creating a hydrophilic surface and remain stable throughout the life span of the implant. B+ features provide superior bone healing and implant integration. The phosphonated molecules have demonstrated high stability in terms of chemical and enzymatic degradation. These properties prevent the molecules from detaching from the implant surface, which allows them to remain present for the lifespan of the implant, ensuring bone attachment throughout each successive bone remodelling cycle.

NBM (Nano Bridging Molecules), a multidisciplinary company based in Switzerland, developed this unique surface. The technology has clinically demonstrated to result in visible bone growth directly on the surface of the B+ implant. The NBM research team performed case studies where B+ had proven very efficient in maintaining bone levels over time.

Firstly, presented in this brochure are the papers published by the NBM team. Following, is the research being conducted by MIS, which includes a series of pre-clinical and clinical studies with the B+ treated implants. They are aimed at examining the features and effects of the B+ surface on various compromised cases and biological processes, including early loading, osseointegration and bone formation.
In the following studies the B+ molecule was referred to as SurfLink, a patented Surface Technology under license from NB Molecules.
A Novel Multi-Phosphonate Surface Treatment of Titanium Dental Implants: A Study in Sheep

Published in ‘Journal of Functional Biomaterials’ 2014, 5, 135-157.
A Novel Multi-Phosphonate Surface Treatment of Titanium Dental Implants: A Study in Sheep

Marcella von Salis-Soglio¹, Stefan Stübinger¹², Michéle Sidler¹³, Karina Klein¹, Stephen J. Ferguson⁴, Käthi Kämpf¹, Katalin Zlinszky¹, Sabrina Buchini⁵, Richard Curno⁵, Péter Péchy⁵, Bjorn-Owe Aronsson⁵, Brigitte von Rechenberg¹

Abstract

The aim of the present study was to evaluate a new multi-phosphonate surface treatment (SurfLink®) in an unloaded sheep model. Treated implants were compared to control implants in terms of bone to implant contact (BIC), bone formation, and biomechanical stability. The study used two types of implants (rough or machined surface finish) each with either the multi-phosphonate Wet or Dry treatment or no treatment (control) for a total of six groups. Animals were sacrificed after 2, 8, and 52 weeks. No adverse events were observed at any time point. At two weeks, removal torque showed significantly higher values for the multi-phosphonate treated rough surface (+32% and +29%, Dry and Wet, respectively) compared to rough control. At 52 weeks, a significantly higher removal torque was observed for the multi-phosphonate treated machined surfaces (+37% and 23%, Dry and Wet, respectively). The multi-phosphonate treated groups showed a positive tendency for higher BIC with time and increased new-old bone ratio at eight weeks. SEM images revealed greater amounts of organic materials on the multi-phosphonate treated compared to control implants, with the bone fracture (from the torque test) appearing within the bone rather than at the bone to implant interface as it occurred for control implants.
Study Design: Surflink®, Sheep Model - removal torque at 2w, 8w and 52w

Fig.1 Mean pairwise relative difference in removal torque values of roughened dry multi phosphonate (Surflink®) treated versus control roughened dry implants by time.
SEM Analysis of Osseointegrated Phosphorous Rich Implants After 52 Weeks in Sheep Pelvis

Presented at the Europerio 8, London, June 3-6, 2015
Aim
The surface of dental implants determines the initial phases of the biological response and affects its ability to integrate into the surrounding tissue. Covalently binding a monolayer of phosphorous rich molecules (SurfLink) to well established surface modifications (sandblasting, acid-etching) offers new dimensions of osseointegration. The aim of this study is to present the surface analysis of SurfLink® implants using Scanning Electron Microscopy (SEM) and elemental analysis (EDX).

Material and Methods
Machined and roughened dental implants with either SurfLink® treatment or no treatment (control) were placed in the pelvis of 24 sheep. Selected implants, retrieved after 52 weeks healing, previously used for removal torque testing, were analyzed by SEM and EDX (Phenom ProX SEM, high-sensitivity backscattered electron detector for topographical mode and thermoelectrically cooled Silicon Drift Detector for EDX).

Results
SurfLink® implants showed increased bone coverage on the machined and roughened surfaces compared to control implants. The presence of mineralized fibrous structures was evidenced by significant Ca and P peaks detected by EDX, with bone cells on the SurfLink® implant surface. The machined control implant showed a nearly bare titanium surface. Fracture lines after torque testing occurred at the bone-implant interface in the control group, while the SurfLink® implants showed a fracture line within the bone, indicating the absence of the typical proteoglycan layer.

Conclusion
SEM images of SurfLink® implants showed fractures within the bone and not at the bone-implant interface. This suggests a significant increase in bone adhesion on SurfLink® surfaces. Clinically this results in improved implant stability especially in the early phases of osseointegration.
Study Design: SurfLink®, Sheep Model - SEM images of torqued implants with adjacent bone after 52w healing

Fig. 1 Longitudinal section with adjacent tissue

Fig. 2 Rough implant (SurfLink), longitudinal section (field of view)

Fig. 3 Adjacent bone tissue, fracture line within the bone (5000x)

Fig. 4 Rough implant - control sample (field of view)

Fig. 5 Rough implant (control sample), longitudinal section (1000x)

Fig. 6 Control, fracture line in the implant-bone interface (5000x)
In the following study the B+ molecule was referred to as SurfLink, a patented Surface Technology under license from NBMolecules.

**SurfLink® Dental Implant: A Novel Implant Surface for Accelerated and Improved Bone Healing**

Published in 'European Cells and Materials' Vol. 23. Suppl. 1, 2012.
SurfLink® Dental Implant: A Novel Implant Surface for Accelerated and Improved Bone Healing

M. von Salis1, B. von Rechenberg1, S. Ferguson2, S. Buchini3, R. Curno2, P. Pechy3, B.-O. Aronsson3

Introduction

SurfLink® Dental is a novel surface treatment by NBMolecules® and has shown the potential to establish a rapid and stable bone-to-implant interface, an essential requirement for successful implant integration and patient prognosis. SurfLink® binds covalently to titanium producing a nanometer thin molecular monolayer. The treated implant is highly hydrophilic by virtue of its biomimetic phosphate-like groups. This results in enhanced biocompatibility. In the clinical situation, such enhanced biocompatibility can be expected to result in increased osseointegration and long-term implant stability, significantly reducing the risk of micromotion and increasing implant success.

Methods

Dental implants with a roughened surface finish with either SurfLink® Dental treatment or no treatment (control) were placed in the left and right pelvis of 24 sheep according to a well-established animal model. Animals were sacrificed after 2, 8 and 52 weeks. Overall integration of SurfLink® Dental implants was assessed by histological, biomechanical and scanning electron microscopy (SEM) evaluations at short and long-term time points.

Results

Implants from all groups were partially or fully surrounded by cortical and cancellous bone after 2, 8 and 52 weeks, as shown by histological analysis. In cancellous bone at 2 weeks, SurfLink® Dental treated implants showed greater integration over control implants, as evidenced both by a higher new bone formation (+43% New/Old bone) and slightly higher Bone-to-Implant Contact (BIC) values (+3%). This is a significant observation, as over time, failure rates are more commonly caused by a lack of implant stability from the cancellous bone. At 8 weeks, SurfLink® Dental treated implants showed a 13% increase in new bone formation over control implants. After 52 weeks bone remodelling appeared to slow down, with mature lamellar bone structures seen around dental implants of all groups. Compared to control implants, SurfLink® Dental treated implants showed a 39 % increase in BIC values. SurfLink® Dental treated implants showed greater integration over control implants with higher torque and stiffness values at 2 weeks (+ 32% and + 37% p≤0.05, respectively). Furthermore, at 52 weeks, long term fixation and stability continued to be reflected by superior torque and stiffness values (+ 7% and + 21%, respectively). SEM observations of SurfLink® Dental implants showed abundant bone coverage with fractures occurring within bone rather than at the bone to implant interface (Fig 3). This indicates a high degree of adaptation and adhesion integrating the treated surfaces with the surrounding bone.

Discussion & Conclusions

In conclusion, SurfLink® Dental was shown to greatly enhance early and long-term implant fixation and overall implant osseointegration.

Study Design: Surflink®, Sheep Model - Bone-Implant Contact percentage at 2w, 8w and 52w

SEM of implants retrieved after 52 weeks showing fracture within bone on SurfLink® Dental treated implant (a), and separation at the bone-to-implant interface on control implants (b).
Multi-Phosphonate Treated Dental Implants: Comparison of Clinical Outcome in Maxilla, Mandible, Smokers and Non-Smokers

Published in 'Clinical Oral Implants Research' 25 (Suppl. 10), 2014
Multi-Phosphonate Treated Dental Implants: Comparison of Clinical Outcome In Maxilla, Mandible, Smokers and Non-Smokers

B.-O. Aronsson¹, I. Dojcinvic², L. Germon¹, N. Levy¹, R. Curno¹, S. Buchini¹, P. Pechy¹

Aim/Hypothesis
The effect of SurfLink® surface treatment of dental implants at 1 year post-loading was further analysed in respect to implant surface (SurfLink® treated vs control implants), implant position (maxilla vs mandible), patient characteristics (smoker vs non-smokers, gender, age), implant dimensions and bone augmentation.

Materials and Methods
The clinical study was conducted in a private Swiss clinic according to GCP and ISO 14155. Prior to the study, no clinical data was available on SurfLink® treated implants and sample size calculation was therefore not conducted. Twenty three patients were enrolled in the study (Ethics Committee Lausanne, approval n° 214/07 and SwissMedic, approval n° 2008-MD-0024) with broad inclusion criteria. Patients requiring at least 2 single implant-supported crowns were randomised according to a split-mouth design to receive one SurfLink® treated implant and one non-treated control implant. Cylindrical titanium grade IV roughened implants with internal connection were used. Single implants were loaded after 3 months in mandibles and 6 months in maxillae. If more than 2 implants were needed, SurfLink® treated implants were placed and restored with single crowns. The study has been un-blinded. The implants were assessed for implant failure, marginal bone level changes, marginal bleeding and other complications. Mesial and distal bone heights were evaluated using x-rays and the changes in bone level were analysed by a Two-Paired-Samples, two-sided, Student t-test with P < 0.05 for significance (RealStatistics plugin for MS Excel 2013). The comparison was carried out as described in the aim.

Results
Twenty three patients were recruited. At 1 year post-loading, there was one drop-out and one patient missed the baseline time point. No implant failures or other complications related to the implants occurred. No marginal bleeding was observed. Marginal bone levels were analysed up to 1 year post-loading. Some of the results are summarised in Table 1, for the 21 patients. When the additional SurfLink treated implants are included in the analysis, a statistically significant difference in marginal bone level changes between the 2 groups is observed (P = 0.033).

Conclusion & Clinical Implications
SurfLink treated dental implants showed statistically significant (P = 0.033) improvement in maintaining marginal bone levels when compared to untreated control implants. This seems to particularly benefit patients with compromised (i.e. smokers) or poor (i.e. maxilla) bone quality.

¹ Nano Bridging Molecules SA, Gland, Switzerland; ² Private Dental Clinic, Morges, Switzerland
### Comparison of Mean Changes on Peri-Implant Marginal Bone Levels at 1 Year Post-Loading Between Implant Types, Positions, and Patient Characteristics

#### Study Design: Surflink®, Maxilla vs. Mandible; Smokers vs. Non-smokers - 1Y Post Loading

|                  | Number of Patients | Implant Type | Mean±SD  |
|------------------|--------------------|--------------|----------|
| **Surface**      | 21                 | SurfLink®    | -1.09±0.76 |
|                  |                    | SurfLink® (a) | -1.04±0.72 |
|                  |                    | Control      | -1.36±0.87 |
| _p_ / _p_ (a)    |                    |              | 0.057/0.033 |
| **Maxilla**      | g(b)               | SurfLink®    | -1.32±0.79 |
|                  |                    | Control      | -1.70±0.59 |
| _p_             |                    |              | 0.070     |
| **Mandible**     | g(b)               | SurfLink®    | -0.92±0.83 |
|                  |                    | Control      | -0.95±1.08 |
| _p_             |                    |              | 0.914     |
| **Smokers**      | 6                  | SurfLink®    | -0.77±0.82 |
|                  |                    | Control      | -1.24±0.82 |
| _p_             |                    |              | 0.062     |
| **Non smokers**  | 15                 | SurfLink®    | -1.22±0.72 |
|                  |                    | Control      | -1.41±0.90 |
| _p_             |                    |              | 0.285     |

Comparison of mean changes on peri-implant marginal bone levels at 1 year post-loading between implant types, position and patient characteristics. (a) The total number of patients included in the analysis is 21. Three patients had one additional SurfLink® treated implants each. For these three patients, the average values of the two SurfLink® treated implants were used in the statistics. (b) Three patients had 1 implant placed in the mandible and 1 implant placed in the maxilla. These patients were excluded from the analysis.
Safety and Efficacy of a Biomimetic Monolayer of Permanently Bound Multi-Phosphonic Acid Molecules on Dental Implants

Published in ‘European Journal of Oral Implantology’ 2013;6(3):227-236.

In the following study the B+ molecule was referred to as SurfLink, a patented Surface Technology under license from NBMolecules.
Safety and Efficacy of a Biomimetic Monolayer of Permanently Bound Multi-Phosphonic Acid Molecules on Dental Implants: 1 Year Post-Loading Results from a Pilot Quadruple-Blinded Randomised Controlled Trial

Marco Esposito¹, Ivan Dojcinovic², Laurence Germon³, Nicole Levy³, Richard Curno³, Sabrina Buchini³, Peter Pechy³, Bjorn-Owe Aronsson³

Purpose
To evaluate the safety and clinical efficacy of a novel surface treatment (SurfLink®, Nano Bridging Molecules, Gland, Switzerland) on titanium dental implants. SurfLink consists of a monolayer of permanently bound multi-phosphonic acid molecules, which mimics the surface of naturally occurring hydroxyapatite.

Materials and Methods
Twenty-three patients requiring at least two single dental implants had their sites randomised according to a split-mouth design to receive one titanium grade 4 implant treated with SurfLink® and one untreated control implant. Additional SurfLink-treated implants were placed if needed. Implants were submerged for 3 months in mandibles and 6 months in maxillae, were loaded with definitive metal-ceramic crowns, and followed up for 1 year after loading. Outcome measures were crown/implant failures, any complication, radiographic peri-implant marginal bone level changes and marginal bleeding.

Results
One patient dropped out after abutment connection. All remaining patients were followed up to 1 year post-loading. No implant failed and only 1 postoperative complication (pain) occurred, but it may not have been related to the implant treatment. No bleeding was observed when a periodontal probe was used to examine the peri-implant soft tissues around the implants. There were no statistically significant differences in marginal bone level changes between the two groups (P=0.057, mean difference=-0.27, SE = 0.13; 95% CI -0.55 to 0.01).

Conclusions
Preliminary short-term data (1 year post-loading) of implants with a biomimetic monolayer of permanently bound multi-phosphonic acid molecules (SurfLink surface treatment) presented no safety issues. Clinical healing in both the control and SurfLink-treated implant group was uneventful and did not differ significantly between groups. More challenging clinical situations need to be investigated to evaluate the real effectiveness of this surface treatment.

¹ Freelance researcher and Associated Professor, Department of Biomaterials, The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
² Private practitioner, Morges, Switzerland; ³ Nano Bridging Molecules, Gland, Switzerland
Study Design: SurfLink®, Split-mouth design; Marginal Bone Loss changes, 1 year post-loading

Fig 1. Box plot representing peri-implant bone loss at different times for SurfLink-treated and untreated control implants (N=21). P values (*paired t test; *Wilcoxon test) between time intervals are indicated.
Surflink® Surface Treatment of Implants Placed in the Posterior Maxilla After Sinus-Floor Elevation

Published in EDJ journal, Issue 2/2014, Vol.10
Objective
In this case study, SurfLink-treated implants were used in the elevated sinus of a smoker with a history of peri-implantitis to show that successful osseointegration can be achieved.

Materials and Methods
A 68-year-old patient with a history of peri-implantitis required rehabilitation of the posterior maxilla. The preoperative examination revealed a 12 mm-wide ridge while the height of the ridge at site 16 was insufficient for a standard implant. Thus, a sinus-floor elevation was planned and performed by opening a lateral window and using granular inorganic bovine bone (Bio-Oss; Geistlich, Wolhusen, Switzerland) and a resorbable collagen membrane (Bio-Guide; Geistlich). No complications occurred during healing.

After six months of healing, two cylindrical SurfLink-treated implants and one nontreated implant were placed at sites 16, 15 and 14, aided by a surgical stent. The implants were properly aligned and remnants of inorganic granules could be observed radiographically. One SurfLink-treated implant and one nontreated implant are currently followed in a quadruple blinded RCT, whose results will be reported later. The second SurfLink-treated implant at site 16 is discussed in this report.

Conclusions
Successful osseointegration was obtained with a SurfLink-treated medium-rough (SLA-type) implant placed in the posterior maxilla after sinus-floor elevation in a heavy smoker with a history of periimplantitis and medium bone quality.
Effect of B+ Surface Treatment on Bacterial Induced Biocorrosion and Metal Ions Release from Ti6Al4V in Vitro

David Kohavi¹, Nir Sterer¹, Eti Shlomo¹

Objective
To examine the effect of B+ surface coating on bacterial induced biocorrosion and metal ions release.

Hypotheses
The use of surface coating of titanium alloys is aimed at increasing implants surface wettability, protein adhesion and bone formation. It is possible that coating the titanium alloy surface may also protect it from bacterial induced biocorrosion.

Study Design
Discs will be placed at the bottom of a 24 well microplate and inoculated with the test bacteria. Wells will be filled with growth media and incubated at 37°C for 7 days.

Following incubation the discs corrosion potential and metal ions release will be analyzed. (Fig1)

Project Status
- Expected data: June 2017.

Fig 1. 15mm Diameter Ti6Al4V Discs with 4 Different Surfaces

¹Tel-Aviv University, Israel
Osteogenic Potential of Different Ti Surfaces

Xiaohui Rausch-Fan\(^1\), Oleh Andrukhov\(^1\)

Objective
To investigate, how recently developed B+ surface treatment influence the behavior and differentiation of osteoblasts compared with two other surfaces with different characteristics.

Hypotheses
The behavior and differentiation of osteoblasts on Ti surface is dependent on surface characteristics. Improved differentiation of osteoblast on Ti surface in vitro might correlate with improved osseointegration and clinical outcome of dental implants in vivo.

Project Status
- Expected data: December 2017.

Study Design: In vitro cell-culture, osteoblast, response to Ti surfaces.

Osteoblasts in vitro

Time Lapse Microscopy

Proliferation Differentiation

\(\text{Control} \quad \text{Sand-Blasted Acid-etched \ B+ treated} \quad \text{Sand-Blasted Acid-etched} \quad \text{Sand-Blasted Acid-etched Modified}\)

1 Medical University of Vienna, Austria
De Novo Bone Formation Around Implants with Different Surface Characteristics. An Experimental Study in the Beagle Dog

Mariano Sanz Alonso¹, Fabio Vignoletti¹, Javier Nuñez¹, Javier Sanz¹, Fernando Luengo¹, Rafael Pla¹, Riccardo de Raimundo¹, Sergio Martinez¹

Objective
To investigate whether B+ implants demonstrate improved histological outcomes in terms of improved osseointegration and maintenance of adequate soft tissue dimensions.

Main Outcome Measurements
- De novo bone formation - Studying the biological sequence of early bone healing around the implants.
- Morphogenesis of the peri-implant mucosa - Studying the formation and dimensions of the peri-implant mucosa.

Project status
- Expected Data - June 2017.

Model: Canine mandible, B+ vs. Control, 2w, 8w, soft tissue and bone healing

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¹University Complutense Madrid, Spain
Experimental Peri-Implantitis Around Implants with Different Surface Characteristics. An Experimental Study in the Beagle Dog

Mariano Sanz Alonso¹, Fabio Vignolletti¹, Javier Nuñez¹, Javier Sanz¹, Fernando Luengo¹, Rafael Pla¹, Riccardo de Raimundo¹, Sergio Martinez¹

Objective
To investigate influence of two different surface treatments, on the progression of experimental peri-implantitis

Main Outcome Measurements
- Progression of experimental peri-implantitis
- Studying the biological sequence of early bone healing around the implants.
- Morphogenesis of the peri-implant mucosa
  - Studying the formation and dimensions of the peri-implant mucosa.

Project Status:
- Expected Data: February 2018.

Study Design: Canine mandible, induced PI, clinical and X-ray, Histology

Week -24  |  Week -12  |  Week 0  |  Week 12  |  Week 24
---|---|---|---|---
Extractions  |  Implantation in Healed Sites  |  Peri-Implantitis Induction  |  Silk Ligatures
Objective
To evaluate the influence of the B+ surface treatment on the early osseointegration of sand-blasted acid-etched dental implants, and to explore the potential benefit of B+ for smokers.

Project Status
- Scheduled start- June 2017

Study Design: Mini-implant human model, 2w and 8w, human histology

- 48 Smokers
- 48 non-smokers

B+ Vs. Regular surface

Implantation of one mini-implant (D:2.5mm, L:6mm) in posterior region of the mandible or of the maxilla

Retrival of mini-implants and the surrounding tissues, with a 4.0-mm-wide trephine bur
Evaluation of B+ Surface in an Early Loading Protocol

Pablo Galindo-Moreno¹, Miguel Padial-Molina¹, Lourdes Gutiérrez Garrido¹, Elena Sánchez Fernández¹, Francisco O’Valle², Andrés Catena³

Objective
To evaluate the safety and efficacy of B+ treated implants in an early loading protocol.

Main outcome measurements
- Success rate of early loaded implants vs. conventionally loaded at 1-year control
- Crestal bone loss of early loaded implants vs. conventionally loaded at 1-year control
- Biomarkers of peri-implant inflammation

Study Design: Clinical study, Early loading, 1-year, Success rate, X-rays and inflammation markers

Expected data: June 2018.
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