

# bonalive

Smart Healing<sup>™</sup>

Introducing a new era of healthcare



Smart Healing™

Bonalive is a smart biomaterials company, transforming healthcare at the intersection of biology and technology. With over 20 years of clinical history, and one of the most evidence-based technologies in the industry, we are re-imagining a smarter future for healthcare.

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Bona Class

Bonalive is an ISO 13485:2016 certified, Class III medical device company. Bonalive® granules, Bonalive® putty and Bonalive® putty MIS are CE marked medical devices.

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Bonalive advances the world's transition to sustainable solutions for infection treatment and bone regeneration. We envision a world where bone infections can be treated without antibiotics – a smarter world, for a smarter life.

# Smart Healing<sup>™</sup>

Antimicrobial resistance (AMR) is one of the greatest challenges facing healthcare today. In the face of growing resistance, we need solutions to an increasingly complex global problem. Solutions, that are smarter and more sustainable for patients worldwide.

Coming to life at the intersection of biology and technology, Smart Healing<sup>™</sup> represents a new standard. A new era for patient care.

As Smart Healing<sup>™</sup> enables increasingly antibiotic free patient care, we provide the world with biomaterial technologies that restore body function through the patient's own biological processes. Restoring and sustaining patient life. Together.



# For patient wellbeing

To enable a faster recovery time, fewer surgeries and a higher quality of life for patients, Smart Healing™ solutions are comprised of natural biological compounds for use in both adult and pediatric patients.



Our solutions aim to minimize the complexity and amount of procedures that medical professionals perform, increasing the capacity of hospital organizations and their personnel to provide better care for more patients.



Smart Healing<sup>™</sup> enables procedures that are more costeffective and more sustainable. By aiming to help solve a global problem through improved patient care, Bonalive is committed to creating a better future for the healthcare ecosystem.



# Our technology



At the core of our technology is S53P4 bioactive glass – a smart biomaterial consisting solely of elements naturally existing in the human body.

Bonalive® S53P4 bioactive glass is osteoconductive and also osteoproductive in the promotion, migration, replication and differentiation of osteogenic cells and their matrix production.\* Bioactive glass S53P4 consists of sodium, silicate, calcium and phosphate.



When Bonalive<sup>®</sup> bioactive glass is placed into the bone cavity, it reacts with body fluids to activate the granules. During this activation period, the bioactive glass goes through a series of chemical reactions, creating the ideal conditions for bone to rebuild through osteoconduction.

- Na, Si, Ca, and P ions are released.
- A silica gel layer forms on the bioactive glass surface.
- CaP crystallizes, forming a layer of hydroxyapatite on the surface of the bioactive glass.

**Picture:** Hydroxyapatite starts to form on Bonalive® granules surface.

## 2. Interaction

(\*) 6-12 WEEKS

Once the hydroxyapatite layer is formed, the bioactive glass interacts with biological entities, i.e. blood proteins, growth factors and collagen. Following this interactive, osteoconductive and osteostimulative\*\* process, new bone grows onto and between the bioactive glass structures.

- Bioactive glass bonds to bone facilitating new bone formation.
- Osteostimulation\*\* begins by stimulating osteogenic cells to increase the remodeling rate of bone.
- Radio-dense quality of bioactive glass allows for post operative evaluation.

**Picture:** Bonalive<sup>®</sup> granules bond to bone and stimulate new bone formation (osteostimulation\*\*).

### 3. Transformation

MONTHS-YEARS

In the final transformative phase, the process of bone regeneration and remodeling continues. Over time the bone fully regenerates, restoring the patient's natural anatomy.

- Bone consolidation occurs.
- Bonalive<sup>®</sup> bioactive glass continues to remodel into bone over a period of years.

**Picture:** Histological 20  $\mu$ m-thick section from the mastoid area a few months after Bonalive® granules implantation.

Pictures 1-2: Courtesy of Turku University Hospital, Finland Picture 3: Courtesy of Päijät-Häme Central Hospital, Finland

# Our products

We offer a range of osteostimulative\* technologies to efficiently and cost-effectively restore patient quality of life. Our products facilitate the filling, reconstruction and regeneration of bone defects in both adult and pediatric patients.

Smart	Healing™
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Bonalive <sup>®</sup> granules	Bonalive <sup>®</sup> putty	Bonalive® putty MIS
A unique bone regeneration echnology that naturally nhibits bacterial growth and stimulates bone formation.	A highly moldable, easy-to- apply bone regeneration technology that naturally stimulates bone formation.	A smart bone regeneration technology, providing stable positioning and controlled access in minimally invasive surgery.
ndications Bone cavity filling Bone cavity filling in the treatment of chronic osteomyelitis Mastoid cavity obliteration	<ul> <li>Intended use</li> <li>Filling, reconstruction and regeneration of bone defects</li> <li>Indications for use</li> <li>Bony voids and gaps</li> </ul>	<ul> <li>Intended use</li> <li>Filling, reconstruction and regeneration of bone defects</li> <li>Indications for use</li> <li>Bony voids and gaps</li> </ul>
<b>Composition</b> 53% SiO <sub>2</sub> 23% Na <sub>2</sub> O 20% CaO 4% P <sub>2</sub> O <sub>5</sub>	Composition • $53\% \text{ SiO}_2$ • $23\% \text{ Na}_2\text{O}$ • $20\% \text{ CaO}$ • $4\% \text{ P}_2\text{O}_5$ • Polyethylene glycols (PEGs) and glycerol	Composition • 53% SiO <sub>2</sub> • 23% Na <sub>2</sub> O • 20% CaO • 4% P <sub>2</sub> O <sub>5</sub> • Polyethylene glycols (PEGs) and glycerol
Properties Inhibition of bacterial growth Osteoconductive, osteostimulative*	<ul> <li>Properties</li> <li>Osteoconductive, osteostimulative*</li> </ul>	<ul> <li>Properties</li> <li>Osteoconductive, osteostimulative*</li> </ul>

# Bonalive® granules

### A unique bone regeneration technology that naturally inhibits bacterial growth and stimulates bone formation.

Bonalive<sup>®</sup> granules is a CE marked Class III medical device, providing a Smart Healing<sup>™</sup> solution for bone infections and bone reconstruction. Bonalive® granules has been proven to naturally inhibit the bacterial growth of up to 50 clinically relevant bacteria strains.\*

The clinical efficacy and performance of the granules has been proven over the past 20 years in orthopedic, trauma, septic surgery and mastoid surgery. Bonalive® granules is verified as safe for use in pediatric surgery and consists only of elements that are naturally present in the human body.

By supporting the reconstruction of anatomical structures in the human body, the biodegradable S53P4 bioactive glass gets gradually resorbed and replaced by bone over a period of years. Bonalive® granules radio-dense quality enables post-operative evaluation, allowing surgeons to monitor the healing of their patients.

#### Gram positive bacteria

- Bacillus cereus
- Bifidobacterium adolescentis
- Clostridium difficile
- Clostridium perfringens
- Clostridium septicum
- Corynebacterium ulcerans
- Enterococcus faecalis • Enterococcus faecium .
- Eubacterium lentum
- Listeria monocytogenes
- Micrococcus sp.
- Peptostreptococcus . anaerobius
- Propionibacterium acnes
- Propionibacterium
- propionicus
- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus agalactiae Streptococcus mutans
- . Streptococcus pneumoniae
- Streptococcus pyogenes
- Streptococcus sanguis
- Methicillin-resistant bacteria
- Pseudomonas aeruginosa
- . Staphylococcus
- Staphylococcus

#### Gram negative bacteria

- Acinetobacter baumannii
- Bacteroides fragilis Bacteroides
- thetaiotaomicron Chryseobacterium
- (former Flavobacterium) meningosepticum
- Enterobacter aerogenes
- Enterobacter amnigenus Escherichia coli
- Fusobacterium
- necrophorum
- Eusobacterium nucleatum
- Haemophilus influenzae
- Klebsiella pneumoniae • Moraxella catarrhalis
- Neisseria meningitidis
- Pasteurella multocida
- Porphyromonas gingivalis
- Prevotella intermedia
- Prevotella melaninogenic
- Proteus mirabilis .
  - Pseudomonas aeruainosa Salmonella typhimurium
- Shiaella sonnei
- Veillonella parvula Yersinia enterocolitica

- aureus (MRSA)
- epidermidis (MRSE)

- Bone cavity filling
- Mastoid cavity



#### Increase in pH



1. Sodium (Na) is released from the surface of the bioactive glass and induces an increase in pH (alkaline environment), which is not favourable for the bacteria, thus inhibiting their growth.

#### For orthopedic, trauma and septic bone surgery

Unit size	Granule size	Ref. no.
5 cc prefilled applicator	1.0-2.0 mm	13330
10 cc prefilled applicator	1.0-2.0 mm	13340

#### For ear surgery

Unit size	Granule size	Ref. no.
2.5 cc prefilled applicator	0.5-0.8 mm	13120
5 cc prefilled applicator	0.5-0.8 mm	13130

\* Leppäranta et al. 2008; Munukka et al. 2008. See references on page 22.

Drago et al. Antimicrobial activity and resistance selection of different bioglass S53P4 formulations against multidrug resistant strains. Future Microbiol. 2015;10(8):1293-9. / Drago et al. In vitro antibiofilm activity of bioactive glass S53P4. Future Microbiol. 2014;9(5):593-601.

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The bacterial growth

inhibiting feature of

Bonalive<sup>®</sup> granules is

### INDICATIONS

- Bone cavity filling in the treatment of

SPECIFICATIONS CE marked

- Class III medical device
- Sterilized
- · Available in different granule and unit sizes





- 2. The released Na. Ca. Si and P ions give rise to an increase in osmotic pressure due to an elevation in salt concentration, i.e. an environment where bacteria cannot grow.
- granules Ο Na, Si, Ca and P ions Body fluids

- Bonalive®

Increase in osmotic pressure



# Bonalive® putty and Bonalive® putty MIS

A highly moldable, easy-toapply bone regeneration technology that naturally stimulates bone formation. Bonalive® putty and Bonalive® putty MIS are bioactive, osteoconductive and osteostimulative\* synthetic CE marked Class III medical devices. The putty is a synthetic bone graft substitute delivered as a sterile and ready-to-use paste, requiring no mixing, moistening or other preparation. The putty is available in an applicator and in a dispenser delivery system.

The putty consists of S53P4 bioactive glass in addition to a synthetic binder, i.e. a blend of polyethylene glycols (PEGs) and glycerol. The binder allows the putty to stay in place during surgery. Following its application, the binder is absorbed in a few days, leaving behind only the bioactive glass, thus permitting tissue infiltration between the bioactive glass to facilitate bone regeneration.

The putty's radio-dense quality enables post-operative evaluation, allowing surgeons to follow the healing of their patients. Bonalive® putty and Bonalive® putty MIS have not been verified as inhibiting bacterial growth.



Bony voids and gaps



SPECIFICATIONS

device

Sterilized

# Bonalive<sup>®</sup> putty MIS

CE marked
 Class III medical

reconstruction and regeneration of bone defects

INTENDED USE

Filling,

#### INDICATIONS FOR USE

• Bony voids and gaps



## For orthopedic, trauma, hand and spine surgery in small and medium size defects.

Unit size	Ref. no.
1 cc prefilled applicator	16110
2.5 cc prefilled applicator	16120
5 cc prefilled applicator	16130
10 cc prefilled applicator	16140

For minimally invasive (MIS) bone surgery, especially hard to reach defects.

Unit size	Ref. no.
1 x 5 cc prefilled cartridge with dispenser	18100
1 x 5 cc prefilled cartridge	18131

# **Cost-to-benefit** ratio of Bonalive<sup>®</sup> granules

In a clinical study conducted with 50 patients

Bonalive<sup>®</sup> S53P4 bioactive glass granules is clinically proven to be a cost-effective and sustainable solution in the treatment of chronic osteomyelitis.

Study groups

Treatment group (T)

Control group (C)

Bone infections are characterized by progressive infection resulting in the destruction of bone. Patients who undergo surgery for septic bone may be hospitalized for long periods of time, often developing a resistance to antibiotics.

In cases where the cavitary defect allows sufficient debridement of the necrotic tissue, the granules can be used in a one-stage procedure. Simultaneous with the inhibiting of bacterial growth, the granules heal the bone cavity by stimulating bone formation. This enables a smarter, more sustainable and cost-effective healing solution, reducing the length of hospital stays, while creating significant value across the entire healthcare ecosystem.\*

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16%

Higher success rate of eradication of infection T. Group: 96%





Fewer follow-up procedures

39%

T. Group: 17.8 days

C. Group: 29.3 days

Shorter hospital stays

T. Group: 11.8 months C. Group: 16.4 months

\* The cost effectiveness of Bonalive® S53P4 bioactive glass granules was measured in a retrospective cohort study, of patients diagnosed with long bone chronic osteomyelitis. The study was carried out at Maastricht University Medical Center+. All the results and cost benefits presented here have been calculated with a minimum of 1 year patient follow-up.

\*\* 40 574€ savings per patient according to incremental cost-effectiveness ratio (ICER)

HOSPITAL COSTS Treatment group Control group Result 19 272 € Hospitalization costs 11 829 € -39% 2 215 € 3 299 € -33% Surgical costs Outpatient costs 1322€ 1439€ -8% MATERIAL COSTS **Biomaterial** costs 2 019 € 369€ 447% 389€ -56% Antibiotic costs 881€ LABORATORY COSTS 1983 € 1141€ 74% Imaging costs 147 € 182 € -19% 347€ Microbiological costs 381€ -9% Bonalive® protocol Antibiotic (PMMA) protocol **Study details** Patients were split into two groups: with a 1-stage surgery with a 2-stage surgery Treatment group (T) • Treatment group: 25 Surgeries: Surgery: patients were treated Surgical debridement Stage 1 Control group (C) with Bonalive® S53P4 Implantation of S53P4 Surgical debridement bioactive glass granules, bioactive glass granules Implantation of in a 1-stage surgery. PMMA beads Antibiotic treatment: Stage 2 Control group: 25 Culture specific • Removal of PMMA beads patients were treated Intravenous 14 days Defect filling with with gentamicin loaded Oral 28 days autologous bone PMMA bead chains, in graft or allograft a 2-stage surgery. Antibiotic treatment: Culture specific Intravenous 14 days • Oral 28 days

6 713€

direct savings per

patient \*\*

16

### 96% success rate

Lab costs

11.5 days shorter hospital stays for patients

24% cost decrease per patient

# Areas of use

Our Smart Healing<sup>™</sup> solutions can be used in both adult and pediatric patients, providing significant benefits to both patients and medical professionals. Areas of use include a wide range of indications that require the filling of bone cavities, voids and gaps as well as the reconstruction or regeneration of bone defects.





post-op

post-op

post-op

**Bone infection: Septic non-union** After thorough debridement and decortication of the bone of the necrotic

area, Bonalive® granules can be used to effectively resolve even the most challenging septic non-unions. Due to the inhibition of bacterial growth. the use of local antibiotics is not necessary, making Bonalive® granules a distinctly sustainable solution for septic non-union procedures.

Case: Septic non-union with Staphylococcus aureus developed 9 months after trauma. The external fixator was removed and an osteotomy of the fibula and the debridement of the septic non-union site was performed after 15 days. The bone gap was grafted with 20 cc Bonalive® granules mixed with an equal amount of autograft. The fixation, which was performed with intramedullary nailing, was removed during a follow-up 18 months later. Bone healing was achieved 6 months after implantation. The soft tissue healed well without any clinical or laboratory signs of infection recurrence. The dynamization of the nail was performed 14 months post-op and the nail was removed 2 years post-op.

Pictures: Courtesy of Istituto Ortopedico Galeazzi, Italy

#### **Bone infection: Chronic osteomyelitis**

Bonalive® granules have proven effective for bone cavity filling in chronic osteomyelitis treatment. In cases where the cavitary defect allows the sufficient debridement of the necrotic tissue, the granules can be used in a one-stage procedure. Simultaneous with the inhibiting of bacterial growth, the granules stimulate bone formation. This enables cost-effective healing and reduces the length of hospital stays.

Case: Careful debridement and the filling of a 100 cc size defect with 48 cc Bonalive® granules mixed with an equal amount of autologous bone in a one-stage procedure. Although a significant part of the anterior cortex of the distal tibia was removed, new cortical bone was formed. At 2.5 years post-op the fusion was stable. Pictures: Courtesy of Turku University Hospital, Finland



Immediate 11 years post-op post-op



post-op



14 months post-op





14 months post-op



The use of Bonalive® granules in trauma surgery is supported by longterm randomized prospective clinical trials with follow-up extending to 11 years, with long-term results comparable to autograft. The solid nature of Bonalive® granules provides specific benefits, such as allowing the granules to be impacted into the bone defect. The granules maintain their volume effectively, hence they do not shrink or expand. Bonalive® granules remodels slowly to bone, thus allowing sufficient time for bone regeneration.

Case: Depressed tibial plateau fracture was filled with 15 cc Bonalive® granules and supported with an anatomical condylar plate. At 11 years post-op, Bonalive® granules has completely remodeled to bone.

Pictures: Courtesy of Turku University Hospital, Finland

#### Spine

Due to restrictions in the local harvesting of bone graft, minimal invasive surgical (MIS) spine fusion procedures limit the use of autograft. The MIS device enables easy access to bone voids or gaps that are difficult to reach with conventional surgical devices. By stimulating new bone formation through osteostimulation\*, Bonalive® putty MIS produces a high but balanced local bone turnover.

Case: MIS fusion in the degenerative spine. The cages and disc space were filled with Bonalive® putty. In addition, a posterolateral fusion was performed on the right side by using autograft mixed with Bonalive® putty. At 3-month post-op, the patient was free from medication and was able to walk 12 km.

Pictures: Courtesy of Turku University Hospital, Finland

### Benign bone tumor

Pediatric orthopedic surgery is a special focus area of Bonalive® products. The long-term use of Bonalive® granules for treating bone defects created by benign bone tumors, e.g. enchondromas, simple cysts and aneurysmal bone cysts, has shown the granules remodel slowly to bone in the grafted area, without disturbing the normal growth of bone in children.

**Case:** Large bone cyst (ABC/UBC) in a 11-year-old child was carefully evacuated and the dead space was filled with 50 cc of Bonalive® granules covered with 5 cc of Bonalive® putty. At 14-month post-op, the distal end of the femur had grown 12 mm and the patient was asymptomatic and active in playing sports.

Pictures: Courtesy of Helsinki University Hospital, Finland

### Mastoid surgery

Long-term studies have shown that mastoid cavities with continuous infections and cleaning difficulties can be successfully obliterated with Bonalive® granules. The bacterial growth inhibiting feature and remodeling profile of the granules enables significant advantages when performing cholesteatoma and mastoid obliteration surgery. In addition, the osteostimulative\* property of Bonalive® granules supports new tissue formation in the mastoid cavity.

Case: The obliteration of a radical mastoid cavity with cholesteatoma. A 76-year-old patient who had undergone a tympanoplasty (canal wall down) and meatoplasty (cartilage) of her left ear 40 years ago. Recurrent secretion which resulted in frequent intervals of treatment every 2 weeks and wearing a hearing aid caused problems. Excessive cholesteatoma was removed and thorough cleaning was performed. The mastoid and attic were obliterated with 3.5 cc of Bonalive® granules. At 14 months, the healing had progressed well but showed a slight retraction towards the attic. At 24 months the meatus was normal, and the patient had no problems wearing a hearing aid.



Pre-op

Contact

# Supporting services

We offer a range of tools and services to support healthcare professionals in using our products. Proactive education and engagement with our network of surgeons, doctors and other medical professionals allows us to swiftly onboard hospital organizations with Bonalive® products.

### References

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Our comprehensive list of references provides data supporting the use of our products in a wide range of indications. Our peer-reviewed references are a valuable resource for professionals interested in our technology and its applications.

- In vitro
- Preclinical
- Clinical
- Book literature

As new studies emerge regularly, the up-to-date reference list can be accessed by request via our website.

Medical education

We offer a range of medical education tools to help familiarize and onboard healthcare professionals with our Smart Healing™ technologies. Our indication specific brochures provide insight into surgical application, product usage and supporting examples of patient cases.

- Live surgeries
- Indication specific brochures
  Medical information services

Submit any questions that may arise to medical.info@bonalive.com **Events** 

We are present at relevant medical conferences each year, where we enable peer-to-peer support and education for healthcare professionals.

- Congresses
- Seminars

Visit the Events page on our website to see where you can find us next.

For more information, visit www.bonalive.com

# Distribution & support tools



Our expanding distribution network currently reaches over 40 markets and we continuously seek new partners to join us in creating better patient outcomes.

To request the location of your nearest distributor, visit www.bonalive.com/distribution Bonalive headquarters

# bonalive

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# References

We have accumulated over 150 references throughout the past two decades. Those presented here provide an overview of the most notable publications and studies. As new studies emerge regularly, the up-to-date reference list can be accessed by request.

#### 150+ references In vitro Preclinical Clinical

#### IN VITRO

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PRECLINICAL

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#### EAR. NOSE AND THROAT Mastoid surgery

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Anatomical, functional and quality-of-life results for mastoid and epitympanic obliteration with bioactive glass S53P4: a prospective clinical study. Bernardeschi D, Pyatigorskaya N, Russo FY, De Seta D,

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Book

ORTHOPEDICS Benign bone tumor

> A prospective randomized 14-year follow-up study of bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors. Lindfors NC, Koski I, Heikkilä JT, Mattila K, Aho AJ. J Biomed Mater Res. 2010;94A(1):157-64.

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### www.bonalive.com

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