LICENSING OPPORTUNITY

MOUTHWASH OF TRICLOSAN-LOADED NANOPARTICLES FOR GINGIVITIS BASED ON PATENTED TECHNOLOGY

- HIGHER MOUTH RESIDENCE TIME → **BETTER CLINICAL EFFICACY**

  Mucoadhesive nanoparticles maintains Triclosan levels above the minimum inhibitory concentration (MIC) up to 8 times longer than commercial standards

- LOWER ABSORPTION TRHOUGH THE MUCOSA → **BETTER SAFETY PROFILE**

  Nanoparticles retain Triclosan in mouth reducing its systemic absorption up to 4 times lower than commercial standards

- **EASY AND COST-EFFECTIVE PRODUCTION** AT LARGE INDUSTRIAL SCALE
- **INTELLECTUAL PROPERTY RIGHTS UNTIL 2031**

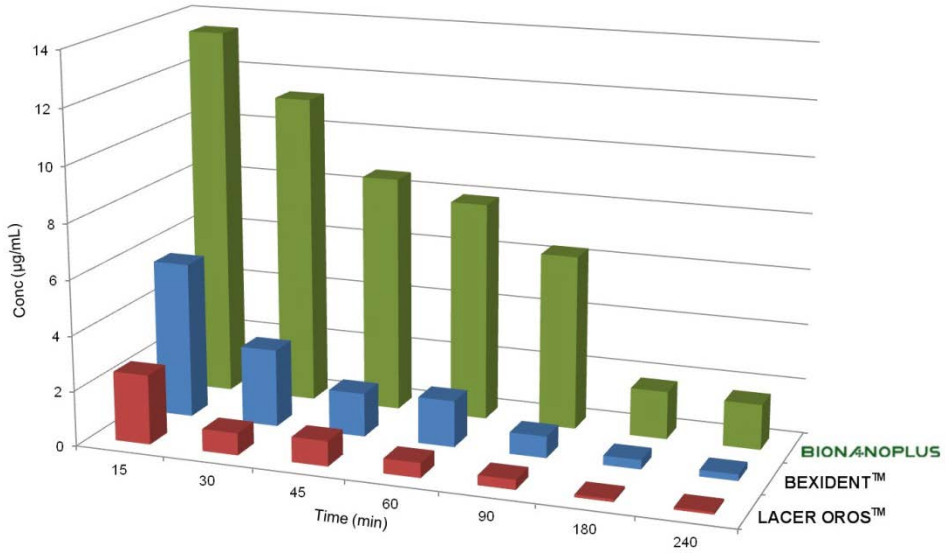

Figure 1: Comparison of Triclosan mouth residence time. Triclosan levels were assessed in saliva samples of human volunteers (n=12). Bionanoplus' formulation maintains Triclosan levels above the MIC for plaque bacteria during 240 minutes. In commercial formulations Triclosan is above the MIC only for 30 - 60 minutes. The MIC is the lowest concentration that will inhibit the growth of a microorganism and for triclosan ranges between 0.2 and 3 µg/mL[1]. LACER OROS™ (Lacer) is a standard formulation of 0.15% Triclosan. BEXIDENT™ (Isdin) is a 0.15% Triclosan formulation with gamma-cyclodextrin to increase the mouth residence time.

HIGHER MOUTH RESIDENCE TIME DUE TO THE COMBINATION OF TRICLOSAN AND GANTREZ TRANSLATES INTO A BETTER CLINICAL EFFICACY

Bionanoplus' Triclosan mouthwash formulation contains Gantrez, a mucoadhesive biocompatible polymer. Gantrez is a non water soluble polymer and thus can offer a sustained release profile. Triclosan-loaded nanoparticles can be easily obtained *in situ* by the addition of water to a mixture of Triclosan and Gantrez. These nanoparticles have a strong adhesive capacity to the oral mucosa which **increases the Triclosan mouth residence time** compared to commercial products. Without Gantrez, Triclosan is rapidly lost from teeth and gums (see Figure 1). The higher residence time of the Bionanoplus' formulation allows maintaining **Triclosan levels above the MIC for bacterial plaque up to 8 times longer** than commercial standards, thus providing a **better clinically efficacy**. It has been clinically demonstrated that the increasing in the mouth residence time due to the combination of Triclosan and Gantrez improves its antiplaque action considerably. A toothpaste containing Triclosan with a two percent of Gantrez is currently commercialized under the trade mark Colgate Total™, the toothpaste number 1 most recommended by dentists and hygienists. This dentifrice has demonstrated significant reductions in microorganisms compared with control dentifrices in a large number of clinical studies[2].

SYSTEMIC EXPOSURE OF TRICLOSAN AFTER ADMINISTRATION IS LOWER THAN COMMERCIAL PRODUCTS THEREFORE NO SYSTEMIC EFFECTS ARE EXPECTED

Despite its higher mouth residence time, nanoparticles retain Triclosan in mouth **reducing its systemic absorption up to 4 times lower** than commercial standards (see Figure 2) and, in consequence, **no safety issues related with systemic exposure** are expected.

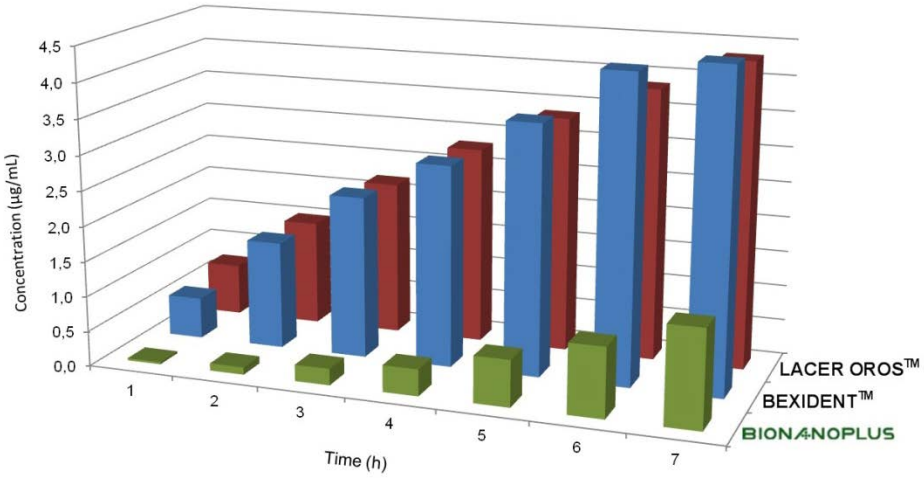

Figure 2: Comparison of Triclosan absorption into the blood. Penetration of Triclosan through the oral mucosa was evaluated in Franz diffusion cells using calf mouth mucosa. The absorption grade was evaluated measuring Triclosan levels in the receptor compartment (similar to blood). LACER OROS™ (Lacer) is a standard formulation of 0.15% Triclosan. BEXIDENT™ (Isdin) is a 0.15% Triclosan formulation with gamma-cyclodextrin to increase the mouth residence time.

BIONANOPLUS' FORMULATION HAS DEMOSTRATED AN ADEQUATE STABILITY PROFILE AT ROOM TEMPERATURE AND CAN BE EASILY AND COST-EFFECTIVE PRODUCED

The mouthwash is a **colloidal suspension** of bioadhesive nanoparticles loaded with Triclosan in which all the excipients are approved by the international regulatory agencies for human use. The exact basic composition of the Triclosan-loaded nanoparticles formulation is showed in the table below. In this formulation, it's possible to add any desired excipients such as Vitamin B5, KNO_3 and so on.

COMPONENT	% w/v
Triclosan (API)	0.15
Gantrez (Polymer)	0.15 – 0.25
Propylene Glycol (Humectant)	5 – 8
Surfactants and aromas	0.5 – 2
Sweeteners	0.5 – 3
Water	75 – 85

The formulation has demonstrated an **adequate stability profile** at room temperature (see table below) and can be **easily and cost-effective produced** at large industrial scale with standard processes of solution preparation.

	Initial Point	1 Year	2 Years
Triclosan Content (% by HPLC)	0.15 ± 0.02	0.15 ± 0.04	0.16 ± 0.03
Precipitation	No	No	No
Aggregation	No	No	No
Color	Slight milky	Slight milky	Slight milky

BIONANOPLUS SEEKS TO LICENSE THE FURTHER DEVELOPMENT AND COMMERCIALIZATION OF ITS MOUTHWASH OF TRICLOSAN-LOADED NANOPARTICLES

Bionanoplus holds the intellectual property rights of this antiseptic mouthwash of nanoparticles loaded with Triclosan worldwide in the patent **PCT/EP2012/056900 (priority date 15/04/2011)**. The second written opinion of the International Preliminary Examining Authority (April 2013) has established novelty, inventive step and industrial applicability in all the key claims.

Bionanoplus seeks to license the further development and commercialization of its Triclosan mouthwash formulation for gingivitis treatment.

The ideal partner would be:

- A company with a strong therapeutic focus in the oral care market.
- Willing to commit investment to develop the product worldwide.
- Marketing experience with capacity to put on the market place the product directly or through alliances.

Bionanoplus is open to different format of partnering modalities including:

- Worldwide exclusive licensing.
- Country based exclusive licensing.
- Opt-in rights + research fee.

BIONANOPLUS FORECAST PEAK SALES OF 27 MILLION EUROS AND ACCUMULATED SALES OF 383 MILLION EUROS IN THE SEVEN MAJOR MARKETS

The anti-gingivitis mouthwash estimated market value in the seven major markets (US, Japan, Germany, France, UK, Italy and Spain) is 890 million Euros. With many players on the market and no clear leader it is difficult to gain a high market share. Nevertheless, Bionanoplus' Triclosan mouthwash formulation presents unquestionable advantages for the patients that should allow it to achieve a significant market share position. Assuming a 3% market share peak, Bionanoplus forecast **peak sales of 27 million** Euros on 2019 – 2025 period and an **accumulated sales of 383 million** Euros in the seven major markets. In addition, its cost-effective production will allow a good profit margin.

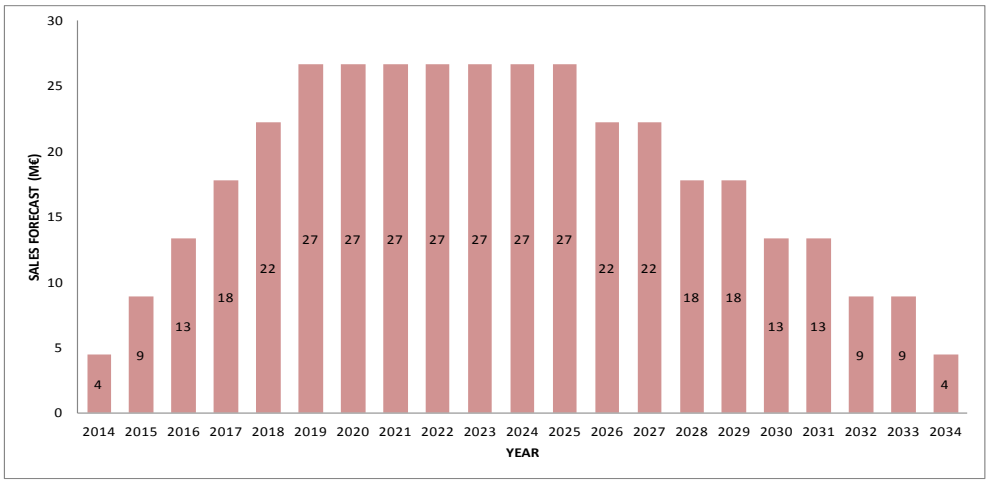

Figure 3: Bionanoplus' Triclosan mouthwash sales forecast in the seven major markets. Forecast of peak sales of 27 million Euros on 2019 – 2025 period and an accumulated sales of 383 million Euros. Hypothesis for market estimation: 1) Market size: 890 million Euros; 2) Market share peak: 3%; 3) Launch: 2014, with an exclusivity period of 17 years

ABOUT TRICLOSAN & GINGIVITS

Triclosan is an antibacterial and antifungal agent that has been used since 1972 to prevent gingivitis. Gingivitis ("inflammation of the gum tissue") is a non-destructive periodontal disease. The most common form of gingivitis is in response to bacterial biofilms (also called plaque) adherent to tooth surfaces, termed plaque-induced gingivitis. In the absence of treatment, gingivitis may progress to periodontitis, which is a destructive form of periodontal disease. In 1997, the U.S. Food and Drug Administration (FDA) reviewed data on Triclosan and found that it was effective in preventing gingivitis.

Triclosan mouthwashes contain 0.15% of the antibacterial ingredient to fight harmful plaque germs, which are the cause of most common dental problems. Common use involves rinsing the mouth with about 15 mL of mouthwash 2 - 3 times a day after brushing. The wash is typically swished or gargled for about a minute and then spat out.

In 2005, some news reports interpreting a study on chlorine disinfection in water treatment plants called into question the safety of some household products that contain Triclosan, including mouthwashes and toothpastes. However, several government agencies around the world such as the FDA and the American Dental Association (ADA) confirm Triclosan's safe use for oral care and recognize that its use provides an important health benefit.

ABOUT BIONANOPLUS

Bionanoplus was founded in 2011 and combines the enthusiasm of a young company with more than 10 years of experience in the nanotechnology and drug delivery fields in academic institutions. Bionanoplus was born in the spirit of avoiding nanoparticles industrial scale-up issues that are decisive factors in many project failures. For this reason, we developed several technology platforms that allow the manufacturing of stable and homogeneous nanoparticles without the use of volatile organic solvents or special equipment, thus ensuring a cost-effectiveness and adequate scalability from laboratory to final production. In addition, all the materials used in the manufacturing of our nanoparticles compile with the regulatory requirements and are present as common excipients in many products.

The staff of Bionanoplus is formed by 8 people with extensive experience in scientific innovation and intellectual property management. Backing us up are more than 50 research articles in peer-reviewed journals and 6 patents.

At the beginning of 2013, Bionanoplus was certified as compliant with the principles of Good Laboratory Practices (GLPs), a new step on the road to excellence on which we are embarked.

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2. Panagakos FS et al. Advanced oral antibacterial/anti-inflammatory technology: A comprehensive review of the clinical benefits of a triclosan/copolymer/fluoride dentifrice. J Clin Dent. 2005;16 Suppl:S1-19.