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Original Article

Self-Adapting Mouthguard with Nano-Hydroxyapatite and Propolis for Early Childhood Caries: Preclinical Safety and Efficacy

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ABSTRACT

The high prevalence of early childhood caries, reaching 80-100% in some regions, highlights the need for safe, convenient products for long-term home remineralization therapy. Existing methods are limited by short enamel contact time, frequent dental visits, and risks associated with high fluoride concentrations in children. This study conducted a preclinical evaluation of the safety and efficacy of an innovative complex for remineralization therapy of initial caries in children. The complex consists of a self-forming thermoplastic mouthguard with time-dependent stiffness relaxation and a gel based on nano-hydroxyapatite and propolis. The study included an *in vitro* cytotoxicity assessment on HS-68 fibroblasts and remineralization potential on 40 demineralized primary teeth and an *in vivo* experiment on 30 Wistar rats evaluating acute and chronic toxicity, local irritant effects, and efficacy in a caries model induced by *Streptococcus sobrinus*. The complex components showed no cytotoxicity (cell viability 86–94%), no acute or chronic toxicity, and no local irritant effects. The gel increased enamel microhardness by 27.3% and raised the Ca/P ratio to 1.62, exceeding values of a standard fluoride gel ($p < 0.05$). In the rat caries model, the gel reduced lesion depth by 64.7% and decreased *S. sobrinus* counts by 2.6 log CFU/mL versus control ($p < 0.01$). The complex combines a high safety profile with proven remineralizing and antibacterial efficacy. The self-forming mouthguard with programmable stiffness relaxation ensures anatomical adaptation and safety for growing jaw tissues. These results support further clinical investigation for long-term home remineralization therapy of initial caries in preschool children.

Keywords: Dental caries, Remineralization therapy, Nano-hydroxyapatite, Propolis, Self-forming mouthguard, Preclinical study

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Introduction

Dental caries remains one of the most common chronic childhood diseases worldwide [1, 2]. According to the World Health Organization, oral diseases affect approximately 3.5 billion people, with caries being the most prevalent [3, 4]. Early childhood caries is recognized as a global public health issue [5]. The situation in the Russian Federation is particularly concerning. Epidemiological studies show high rates of caries among children [6]. In the Omsk region, the prevalence reaches 81% across all age groups, with an

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average intensity of 4.0 decayed teeth per child. In Moscow, among children aged one to five years seeking dental care, the prevalence is 100%, and the dmft index reaches 5.59, indicating extremely high caries activity. According to Russian researchers, caries affects more than 30% of three-year-old children. By age six to seven, this figure rises to 65%. Thus, most children already have carious lesions by the time they enter school.

Caries progression in preschool children is notably rapid. The enamel of primary teeth is immature and continues to mineralize for several years after eruption, making it highly susceptible to cariogenic factors. Without timely intervention, demineralization foci quickly progress to cavitated defects, often leading to pulpitis and periodontitis at an early age [7]. The consequences of early childhood caries extend beyond the oral cavity. Chronic odontogenic intoxication negatively affects the child's general health. Pain disrupts sleep and appetite, while impaired chewing leads to digestive problems [8-17]. Speech disorders may affect socialization, and psychological discomfort reduces the quality of life for both the child and family [18]. Moreover, premature loss of primary teeth creates risks for malocclusion.

Pediatric dentists have a wide range of tools and methods for caries management. Preventive strategies include systemic and topical fluoride application, fissure sealing, professional oral hygiene, and oral care instruction [19]. For treating initial caries (white spot lesions), remineralizing agents based on fluorides, hydroxyapatite, and amorphous calcium phosphate are commonly used, along with resin infiltration. Numerous studies confirm the effectiveness of fluoride varnishes and gels [20]. Silver diamine fluoride also shows high efficacy for arresting carious lesions in children [7, 21]. However, existing methods have several limitations, particularly in pediatric practice. Most remineralizing agents require application in a dental clinic, increasing the number of visits. Each visit creates additional stress for the child and raises time and financial costs for the family. Application methods using standard mouthguards have drawbacks: standard mouthguards often lack a tight seal and do not fit the individual child's jaw anatomy, while custom trays made in a dental laboratory require complex laboratory steps, limiting accessibility and increasing costs [22]. The use of high fluoride concentrations in young children carries risks, including fluorosis and toxicity if accidentally swallowed [20, 23]. Therefore, pediatricians and dentists exercise caution when prescribing such products. A key problem is the low compliance of preschool patients. Children cannot retain applicators in their mouths for extended periods, and parents often cannot supervise multiple daily procedures. This reduces the effectiveness of even the most advanced products [22].

In recent years, innovative approaches to remineralization therapy have emerged globally. One promising direction is the use of nano-sized hydroxyapatite. Nano-hydroxyapatite has high bioavailability, and its crystal structure is identical to natural enamel, allowing it to integrate into the tooth surface and restore mineral density [24-27]. Studies show that nano-hydroxyapatite is as effective as fluorides but without their toxic effects [25, 27]. Another direction involves natural antibacterial components. Propolis and its derivatives exhibit high activity against *Streptococcus mutans*, the primary caries pathogen, without disrupting the oral microbiome, unlike synthetic antiseptics [28-32]. Xylitol has also proven effective as a preventive agent, creating osmotic imbalance in bacteria and stimulating salivation [33-35]. Innovations in application systems represent another area of development. Traditional mouthguards require laboratory fabrication from impressions, making them expensive and inaccessible for widespread use. Modern shape-memory materials allow the creation of self-adapting devices [36-38]. Users can activate such materials at home: when heated to a specific temperature, the material becomes plastic, and after insertion into the mouth and cooling, it takes a precise anatomical shape. This enables personalized therapy without the involvement of a dentist. Polymers with programmable mechanical properties are of particular interest [36, 37, 39, 40]. Such materials can be rigid at the start of use to ensure a tight seal, then become elastic after several hours, eliminating prolonged pressure on tissues. This is especially important in pediatric practice, where any prolonged pressure on a growing jaw may have orthodontic consequences. However, no comprehensive solution currently combines all these innovations in a single product. There is no system that integrates a self-adapting mouthguard with controlled stiffness and a gel based on natural components with proven remineralizing efficacy. Approaches to long-term home therapy designed for course use over several months are also underdeveloped.

As a result, there is an obvious need for a fresh approach to pediatric remineralization therapy. Such a strategy should allow active substances to be in continuous contact with enamel, ideally overnight, without the requirement for a dental visit. The gadget must use self-adaptation to obtain anatomical precision. The composition must be safe and suitable for use in youngsters, with no hazardous effects, and

the application should be simple and convenient for at-home use.

This study aimed to provide a preclinical rationale for the safety and efficacy of an innovative complex for remineralization therapy of initial caries in children, comprising a self-forming thermoplastic mouthguard with time-dependent stiffness relaxation and a gel based on nano-hydroxyapatite and propolis. The gel is positioned as a medicinal product for topical use in dentistry.

Materials and Methods

Study design

The study was conducted in accordance with the requirements for preclinical studies of medicinal products for topical use. The design included several sequential stages: theoretical calculations and component selection, *in vitro* studies (cytotoxicity and remineralization potential), and *in vivo* studies in laboratory animals. Clinical studies in adult volunteers and children are planned as the next stage of development and are not presented in this work. A diagram of the stepwise plan, including product composition, research methods, expected results, control points, and timeframes, is shown in **Figure 1**.

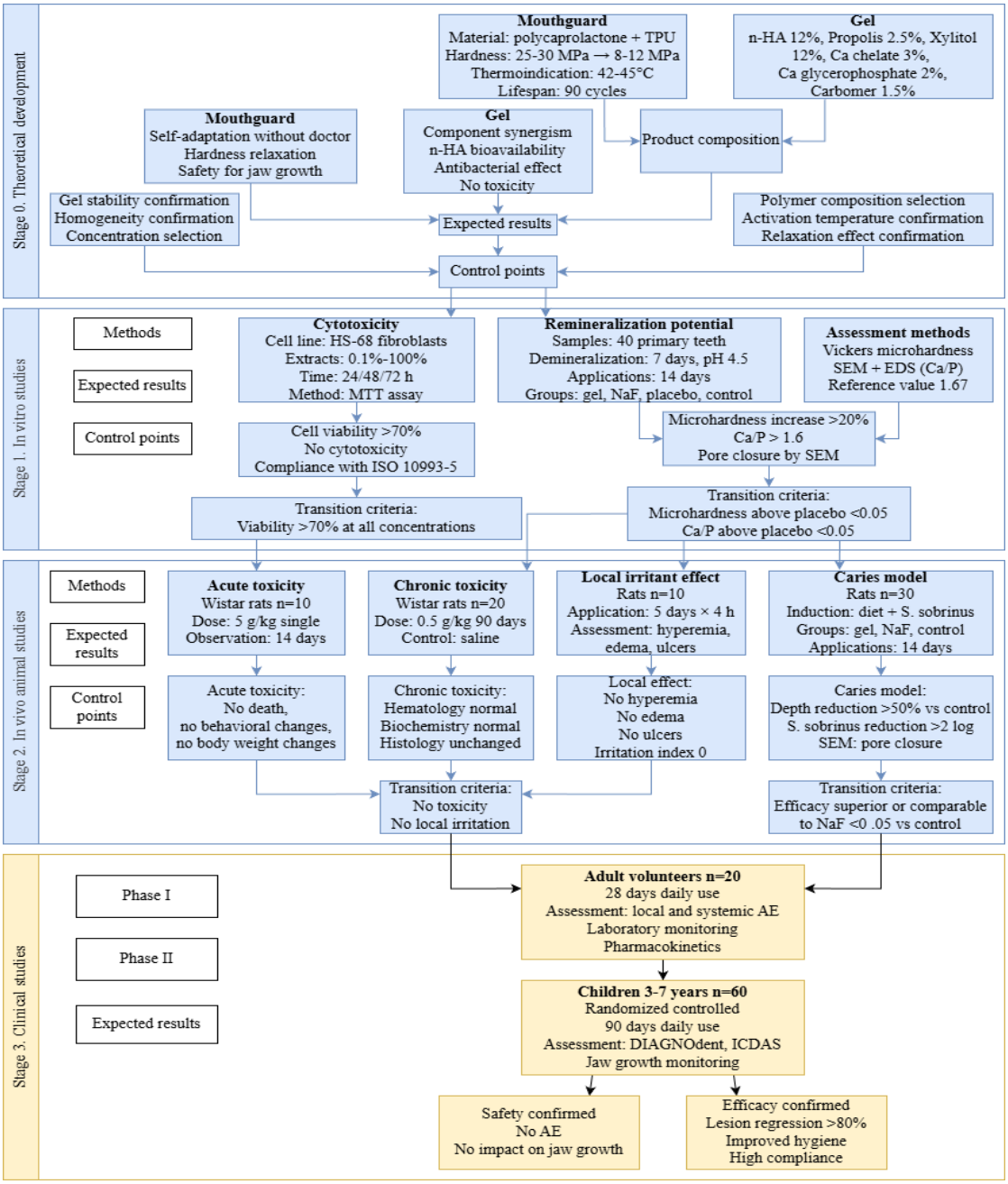


Figure 1. Stepwise development and research plan of the complex. Stages completed in the present study are highlighted in blue. Stages planned for future clinical studies are highlighted in yellow.

Product composition

The treatment set consists of two components: a self-forming thermoplastic mouthguard and a remineralizing gel. It is designed for course use at home.

Mouthguard "BioForm Fit 3D."

The mouthguard is made of modified polycaprolactone with a thermoindicator. The material has temperature memory. When heated to 42–45°C, the polymer becomes plastic. The user inserts the mouthguard into the oral cavity, and under biting pressure it takes the exact anatomical shape. Upon cooling to 36°C, the shape is fixed. The material is programmed for gradual changes in mechanical properties. During the first 2–3 hours of wear, the elastic modulus is 25–30 MPa, ensuring a tight seal. After 4–6 hours, the elastic modulus drops to 8–12 MPa, and the mouthguard becomes elastic. This eliminates prolonged pressure on growing jaw tissues. A thermochromic pigment in the material changes color when the activation temperature is reached. This allows the user to control readiness without a thermometer [41-50]. The mouthguard is designed for 90 use cycles, corresponding to three months of daily use.

Gel "BioForm Kids."

The gel is developed as a medicinal product for topical use in dentistry. Its composition is optimized for prolonged contact with enamel (up to 8 hours). All components are approved for use in children **(Table 1).** A 50 mL bottle of gel is designed for 90 applications (0.5 mL per jaw). Thus, one bottle provides a full three-month course of daily use.

Table 1. Composition of the BioForm Kids gel

Component	Concentration	Functional rationale
Nano-hydroxyapatite (n-HA)	12.0 g	Biomimetic remineralization. Particles of 20–80 nm penetrate enamel micropores. Crystal structure identical to natural enamel.
Standardized propolis extract	2.5 g	Antibacterial activity against *Streptococcus mutans*. Anti-inflammatory effect. Does not disrupt the oral microbiome.
Xylitol	12.0 g	Osmotic effect suppressing bacterial growth. Stimulates salivation. Extends remineralization time. Improves taste.
Amino acid calcium chelate	3.0 g	Highly bioavailable calcium. Provides ion exchange in demineralization foci.
Calcium glycerophosphate	2.0 g	Phosphorus source for hydroxyapatite formation. Synergist with nano-hydroxyapatite.
Carbomer	1.5 g	Forms a viscous base. Provides adhesion to enamel and mouthguard. Ensures prolonged release of active components.
Purified water	to 100 g	Solvent.

In vitro studies

Cytotoxicity assessment

Cytotoxicity was evaluated on human skin fibroblast culture (HS-68 line). Extracts of the BioForm Kids gel and mouthguard material were prepared in DMEM medium at 37°C for 24 hours at concentrations of 0.1%, 1%, 10%, and 100%. Cells were incubated with extracts for 24, 48, and 72 hours. Viability was assessed using the MTT assay, with optical density measured on a plate reader at 570 nm. The criterion for non-toxicity was a reduction in viability of less than 30% relative to control (ISO 10993-5) [51, 52].

Remineralization potential assessment

Forty extracted primary molars were used. Demineralization foci were created on the buccal surface in 0.1 M lactic acid solution (pH 4.5) for 7 days. Samples were divided into four groups of 10 teeth each: main (BioForm Kids gel), comparison (0.05% NaF), placebo (vehicle gel), and control (no treatment). Applications were performed daily for 14 days in a thermostated chamber at 37°C. For the main group, application time was 8 hours (simulating overnight wear); for the comparison and placebo groups, it was 15 minutes (simulating the standard protocol).

Enamel microhardness was measured before and after the experiment using a Vickers microhardness tester (50 g load, 10 seconds). Surface morphology was assessed using scanning electron microscopy (JSM-IT500, JEOL) at ×2000 and ×5000 magnification. The calcium-to-phosphorus ratio (Ca/P) was determined by energy-dispersive X-ray spectroscopy (Oxford X-Max) [53].

In vivo studies

All animal experiments were approved by the Ethics Committee for Laboratory Animal Use (Protocol No. 12/24 of February 5, 2024). Thirty Wistar rats weighing 180–220 g were used. Animals were kept under standard vivarium conditions.

Acute and chronic toxicity assessment

For acute toxicity, the gel was administered once intragastrically at a dose of 5 g/kg (100 times the estimated daily dose for a child). Animals (n=10) were observed for 14 days. For chronic toxicity, the gel was administered daily for 90 days at a dose of 0.5 g/kg (therapeutic dose). A control group (n=10) received saline. At the end of the experiment, hematological and biochemical blood parameters were assessed, and histological examination of the liver, kidneys, spleen, and oral mucosa was performed.

Local irritant effect assessment

The gel was applied to a gauze swab and fixed on the buccal mucosa of 10 rats. Applications were performed daily for 5 days for 4 hours each. The vehicle gel served as a control on the opposite cheek. Hyperemia, edema, and ulceration were assessed at 1, 24, 48, and 72 hours after the last application using a 4-point scale.

Efficacy assessment in a caries model

Caries was induced in 30 rats from day 14 of life. Animals received a cariogenic diet (Diet 2000 with 56% sucrose) and three inoculations of *Streptococcus sobrinus* (strain 6715) [54-56]. After 21 days, animals were divided into three groups of 10 each: main (BioForm Kids gel), comparison (0.05% NaF), and control (no treatment). Applications were performed daily for 14 days. After euthanasia, caries lesion depth was assessed using the Keyes method [57]. Microbiological analysis of tooth swabs included counting *S. sobrinus* colony-forming units on selective media. Enamel morphology of molars was assessed by scanning electron microscopy.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 26.0 and R 4.2.1. Sample size for animal experiments (n=10 per group) was calculated based on 80% power and an expected effect size of 1.2 (Cohen's d) at a significance level of $\alpha = 0.05$ (G*Power 3.1) [58]. Data are presented as mean ± standard deviation (M ± SD). Intergroup comparisons were performed using one-way analysis of variance (ANOVA) with Tukey's post hoc test [59]. Fisher's exact test was used for categorical variables. Differences were considered statistically significant at $p < 0.05$ and highly significant at $p < 0.01$.

Results and Discussion

In vitro studies

Cytotoxicity

Cytotoxicity of the BioForm Kids gel and mouthguard material was evaluated on HS-68 fibroblasts using the MTT assay. After 72 hours of incubation with gel extracts, cell viability ranged from 86% to 94% of control, depending on concentration. The greatest reduction (86%) was at 100% extract and the smallest (94%) at 0.1%. For mouthguard extracts, viability was 88–92%. A reduction below 30% meets ISO 10993-5 requirements. Both components were therefore non-toxic *in vitro*.

Remineralization potential

Forty extracted primary molars with artificial demineralization were divided into four groups: main (BioForm Kids gel), comparison (0.05% NaF), placebo (vehicle gel), and control (no treatment). Applications were performed daily for 14 days (8 hours for the main group, 15 minutes for comparison and placebo). Enamel microhardness (Vickers), surface morphology (SEM), and Ca/P ratio (EDS) were assessed **(Table 2).**

Table 2. Enamel microhardness and Ca/P ratio

Group	Microhardness before (HV)	Microhardness after (HV)	Increase (%)	Ca/P (M ± SD)
Main (BioForm Kids gel)	245 ± 12	312 ± 10	27.3	1.62 ± 0.03
Comparison (0.05% NaF)	248 ± 11	298 ± 12	20.2	1.58 ± 0.04
Placebo (vehicle gel)	247 ± 10	252 ± 11	2.0	1.44 ± 0.05
Control (no treatment)	246 ± 12	240 ± 10	–2.4	1.42 ± 0.04

Note: Data are presented as mean ± standard deviation (M ± SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) with Tukey's post hoc test.

In the main group, microhardness increased by 27.3% (from 245 ± 12 to 312 ± 10 HV), versus 20.2% in the comparison group ($p < 0.05$). The placebo group showed no significant change (+2.0%, $p > 0.05$ vs. control), while the control group decreased by 2.4%.

Ca/P ratio in the main group (1.62 ± 0.03) approached the healthy enamel reference (1.67), significantly higher than in the comparison group (1.58 ± 0.04, $p < 0.05$) and highly significantly higher than in placebo (1.44 ± 0.05) and control (1.42 ± 0.04) ($p < 0.01$).

SEM confirmed these findings. In the main group, enamel surfaces were smooth and homogeneous; micropores were closed, with a layer of newly formed hydroxyapatite. The comparison group showed

improved morphology, but some exposed prisms remained. Placebo and control groups exhibited pronounced demineralization: surface loosening, exposed prisms, and micropores [60, 61].

In vivo studies

All animal experiments were approved by the Ethics Committee (Protocol No. 12/24, February 5, 2024). Thirty Wistar rats (180–220 g) were used.

Acute and chronic toxicity

For acute toxicity, 10 rats received a single intragastric dose of gel at 5 g/kg (100× the estimated pediatric daily dose). No deaths occurred over 14 days. Behavior, activity, food/water intake, and body weight remained normal. For chronic toxicity, 20 rats were divided into a main group (gel 0.5 g/kg daily for 90 days) and a control group (saline). Hematological and biochemical parameters, as well as histology of the liver, kidneys, spleen, and oral mucosa, were examined **(Table 3).**

Table 3. Hematological and biochemical parameters after 90 days (M ± SD)

Parameter	Main group (n=10)	Control group (n=10)	p
Erythrocytes (×10¹²/L)	7.8 ± 0.4	7.9 ± 0.4	>0.05
Leukocytes (×10⁹/L)	8.2 ± 1.1	8.0 ± 1.0	>0.05
Hemoglobin (g/L)	142 ± 8	145 ± 7	>0.05
ALT (U/L)	42 ± 6	40 ± 5	>0.05
AST (U/L)	98 ± 12	95 ± 10	>0.05
Creatinine (μmol/L)	52 ± 6	50 ± 5	>0.05
Urea (mmol/L)	6.2 ± 0.8	6.0 ± 0.7	>0.05
Total protein (g/L)	68 ± 5	70 ± 4	>0.05

Note: Data are presented as mean ± standard deviation (M ± SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) with Tukey's post hoc test.

No significant differences were found between groups ($p > 0.05$). Histology revealed no inflammation, dystrophy, necrosis, or fibrosis; tissue structure was normal.

Local irritant effect

In 10 rats, the gel was applied to the buccal mucosa for 4 hours daily over 5 days. No hyperemia, edema, or ulceration was observed at 1, 24, 48, or 72 hours after the last application. The irritation index (4-point scale) was 0 at all-time points. The vehicle gel also caused no irritation.

Efficacy in the rat caries model

Caries was induced in 30 rats from day 14 of life using a cariogenic diet (Diet 2000, 56% sucrose) and three inoculations of *Streptococcus sobrinus* (strain 6715). After 21 days, animals were divided into three groups (n=10 each): main (BioForm Kids gel), comparison (0.05% NaF), and control (no treatment). Applications were performed daily for 14 days. Lesion depth (Keyes method), *S. sobrinus* CFU counts, and enamel morphology (SEM) were assessed **(Table 4).**

Table 4. Efficacy parameters in the rat caries model

Group	Lesion depth (Keyes score)	*S. sobrinus* (log CFU/mL)
Main (BioForm Kids gel)	1.2 ± 0.3	3.2 ± 0.5
Comparison (0.05% NaF)	2.1 ± 0.4	4.1 ± 0.6
Control (no treatment)	3.4 ± 0.5	5.8 ± 0.7

Note: Data are presented as mean ± standard deviation (M ± SD) where applicable. Statistical analysis was performed using one-way analysis of variance (ANOVA) with Tukey's post hoc test.

In the main group, lesion depth was 1.2 ± 0.3, significantly lower than in the comparison (2.1 ± 0.4, $p < 0.05$) and control groups (3.4 ± 0.5, $p < 0.01$). This represents a 64.7% reduction versus control. *S. sobrinus* counts were 3.2 ± 0.5 log CFU/mL in the main group, significantly lower than in the comparison (4.1 ± 0.6, $p < 0.05$) and control groups (5.8 ± 0.7, $p < 0.01$), a reduction of 2.6 log CFU/mL. SEM of rat molars showed smooth enamel surfaces with hydroxyapatite deposition and closed micropores in the main group [62, 63]. The comparison group showed improvement but with some remaining demineralized areas. The control group had deep enamel destruction with exposed dentin [64, 65].

Table 5 summarizes the overall preclinical safety results.

Table 5. Summary of safety data

Study	Object	Result
In vitro cytotoxicity (gel)	HS-68 fibroblasts	Viability 86–94%, non-toxic
In vitro cytotoxicity (mouthguard)	HS-68 fibroblasts	Viability 88–92%, non-toxic
Acute toxicity	Wistar rats	No deaths, no behavioral changes or weight loss
Chronic toxicity	Wistar rats	Hematology, biochemistry, histology normal
Local irritant effect	Wistar rats	No hyperemia, edema, ulceration (index 0)

Thus, the developed complex demonstrates high safety and proven efficacy. The BioForm Kids gel and mouthguard material are non-cytotoxic, show no acute or chronic toxicity, and cause no local irritation. In the rat caries model, the gel produced a more pronounced remineralizing and antibacterial effect than the reference fluoride product [60, 62, 66].

This study shows the findings from a preclinical evaluation of a novel complex for remineralization therapy of primary caries in children. The complex is made up of a self-forming thermoplastic mouthguard with time-dependent stiffness relaxation and a nano-hydroxyapatite and propolis gel. The data show that this product is highly safe and effective, making it a promising alternative to current techniques for preventing and treating early caries in preschool children [67, 68].

A key *in vitro* finding was the absence of cytotoxicity for both the gel and the mouthguard material. Fibroblast viability exceeded 85% at all tested extract concentrations, meeting international biocompatibility standards [51, 52]. These results align with published data showing that nano-hydroxyapatite and polycaprolactone are safe for oral tissues [60, 66]. The lack of cytotoxicity is essential for advancing the product to clinical trials, especially given the intended use in children, a vulnerable population.

The remineralizing potential of the BioForm Kids gel was confirmed on demineralized primary teeth. Microhardness increased by 27.3% in the main group, significantly exceeding the 20.2% increase observed with a standard fluoride gel ($p < 0.05$). The Ca/P ratio reached 1.62, approaching the reference value for healthy enamel (1.67). This confirms the high bioavailability of nano-hydroxyapatite, whose crystal structure is identical to natural enamel, allowing integration into the tooth surface [60, 61]. Published studies report that nano-hydroxyapatite increases enamel microhardness by 15–25% in similar models, with our results at the upper end of this range. Moreover, nano-hydroxyapatite has been shown not only to restore mineral density but also to form a protective layer against further demineralization [69].

The antibacterial effect of the gel is particularly noteworthy. In the rat caries model, *S. sobrinus* counts decreased by 2.6 log CFU/mL compared to control, significantly outperforming the fluoride reference ($p < 0.05$). This effect is attributed to synergy between propolis, which has well-documented activity against cariogenic streptococci [62, 63, 70], and xylitol, which creates osmotic imbalance and inhibits bacterial adhesion to the pellicle [64, 65]. Unlike synthetic antiseptics, neither component disrupts the oral microbiome—a critical advantage for pediatric use, where dysbiosis risks limit the use of broad-spectrum antimicrobials [71]. Published data show that propolis-based formulations typically reduce *S. mutans* counts by 1.5–2.0 log CFU/mL [63, 70], while our gel achieved a 2.6 log reduction, indicating a more pronounced effect.

Preclinical safety assessment in Wistar rats revealed no acute or chronic toxicity and no local irritant effects. Hematological, biochemical, and histological parameters remained normal after 90 days of gel administration at doses exceeding the therapeutic level [54-57]. These findings are consistent with published safety profiles of nano-hydroxyapatite and propolis [60, 62, 72]. The high safety margin is particularly important for pediatric drug development, where safety requirements are substantially more stringent than for adults [73-76].

The innovation of this complex extends beyond the gel composition to the mouthguard design. Traditional application systems either require laboratory-fabricated custom trays (costly and inaccessible) or use standard mouthguards (poor anatomical fit). Our polycaprolactone mouthguard with temperature memory allows parents to form a custom device at home. Thermoindication (color change) prevents mucosal burns, and programmed stiffness relaxation after 3–4 hours of wear ensures safety for growing jaw tissues [66, 77]. This approach aligns with the shift toward personalized medicine, moving from clinic-based procedures to home-based technologies without compromising efficacy or safety [78].

Another important feature is the set configuration for a three-month course. One 50 mL gel bottle and one

mouthguard provide 90 daily applications—a complete remineralization course. This design enhances parental convenience and ensures treatment continuity, preventing interruptions caused by the need for additional purchases. Regular mouthguard replacement every three months serves two purposes: it prevents biofilm accumulation on the polymer surface and allows adaptation to the child's jaw growth [77, 79].

Several constraints should be recognized. First, this is a preclinical study. Although the rat caries model has been thoroughly validated, it does not fully reflect the synergistic impact of the mouthguard-gel combination since mouthguards cannot be utilized in rodents [54-57]. Only the gel component was tested in vivo. Future clinical trials will analyze the combined effect. Second, controlled clinical trials are required before extrapolating preclinical data to humans. However, the positive in vitro and in vivo results are adequate to warrant further human investigations [79]. Third, the sample size in animal experiments is small (n=10 per group), but it was predicted to have 80% power with an expected effect size of 1.2, ensuring appropriate statistical reliability [58]. Future clinical trials will use bigger sample sizes (up to 60 participants in the pediatric phase).

Future development will proceed in two clinical phases. Phase I will involve adult volunteers to confirm safety, tolerability, and pharmacokinetics. Phase II will include children aged 3–7 years with initial caries to evaluate clinical efficacy using laser fluorescence (DIAGNOdent) and visual assessment (ICDAS), along with cephalometric analysis to definitively confirm that the mouthguard does not affect jaw growth [77, 79].

In conclusion, this preclinical study demonstrates that the developed complex combines a high safety profile with proven remineralizing and antibacterial efficacy. The use of nano-hydroxyapatite and propolis enables biomimetic enamel restoration without the risks associated with high fluoride concentrations [60, 61, 72]. The self-forming mouthguard with controlled stiffness addresses anatomical adaptation and safety for growing tissues [66, 77]. The three-month course configuration makes the product suitable for long-term home use [79]. These findings support further clinical investigation of the complex as a long-term home remineralization therapy for initial caries in preschool children [67, 68].

Conclusion

This preclinical study of an innovative complex for remineralization therapy of initial caries in children, comprising a self-forming thermoplastic mouthguard with time-dependent stiffness relaxation and a gel based on nano-hydroxyapatite and propolis, allows the following conclusions.

The complex demonstrated a high safety profile at all stages of preclinical evaluation. *In vitro*, neither the gel nor the mouthguard material showed cytotoxicity against human skin fibroblasts: cell viability exceeded 85% at all tested extract concentrations, meeting international biocompatibility standards. *In vivo* in Wistar rats, no acute or chronic toxicity was observed after prolonged (90 days) gel administration at doses well above the therapeutic level. Hematological and biochemical parameters did not differ from control values, and histology of internal organs and oral mucosa revealed no pathological changes. Local irritant effects were completely absent: gel application to the buccal mucosa caused no hyperemia, edema, or ulceration, and the irritation index was 0 at all-time points.

The complex's efficacy has been proven in vitro and in vivo. In a demineralized primary tooth model, the BioForm Kids gel enhanced microhardness by 27.3%, which was much higher than the 20.2% rise seen with a normal fluoride gel. The enamel Ca/P ratio reached 1.62, which is close to the recommended value for healthy enamel. Scanning electron microscopy revealed micropore closure and a homogeneous coating of newly generated hydroxyapatite. In a rat caries model caused by Streptococcus sobrinus, the gel had a strong antibacterial effect: bacterial load decreased by 2.6 log CFU/mL compared to the control, greatly surpassing the reference group. Caries lesion depth was 64.7% lower in the main group compared to the control group.

The innovativeness of the complex lies in three key aspects. First, the self-forming polycaprolactone mouthguard with thermoindication allows parents to create a custom application device at home without a dentist, while programmed stiffness relaxation after 3–4 hours of wear ensures safety for growing jaw tissues. Second, the gel based on nano-hydroxyapatite and propolis provides biomimetic enamel restoration without the risks associated with high fluoride concentrations and does not disrupt the natural oral microbiome. Third, the three-month course configuration (one mouthguard and one 50 mL gel bottle, sufficient for 90 applications) makes the product convenient for long-term home therapy and ensures predictable results.

The results of this preclinical study provide a sufficient basis for proceeding to the next stage of development—clinical trials. Two phases are planned: Phase I in adult volunteers to confirm safety and assess

pharmacokinetics and Phase II in children aged 3–7 years with initial caries to evaluate clinical efficacy and definitively confirm the absence of mouthguard impact on jaw growth.

Thus, the developed complex represents a promising option for long-term home remineralization therapy of initial caries in preschool children, combining a high safety profile, proven efficacy, and ease of use.

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Conflict of Interest: None

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Ethics Statement: This study was conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki (2013 revision) where applicable. The animal study protocol was approved by the Ethics Committee for Laboratory Animal Use of the North Ossetian State Medical Academy. All animal procedures were performed in compliance with the ARRIVE guidelines and the Russian Federation legislation on laboratory animal welfare. Animals were housed under standard vivarium conditions with free access to food and water. All efforts were made to minimize animal suffering and to reduce the number of animals used.

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