A 3-month randomized trial evaluating the effects of stannous fluoride bioavailability on gingivitis

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Abstract: Purpose: To assess the impact of formulation chemistry on gingivitis effects of two experimental 0.454% stannous fluoride (SnF_2) dentifrices with low tin bioavailability versus positive and negative controls. **Methods:** Adults with gingivitis were enrolled in this double-blind, parallel group, randomized clinical trial. Gingivitis was assessed with the Löe-Silness Gingivitis Index (LSGI) at baseline, 1 month, and 3 months. The four treatments were: experimental dentifrice A (0.454% SnF_2, pH 4.7, soluble tin = 592 ppm), experimental dentifrice B (0.454% SnF_2, pH 5.8, soluble tin = 102 ppm), positive control (0.454% SnF_2 commercial dentifrice, soluble tin = 2,037 ppm), and negative control (0.76% sodium monofluorophosphate, soluble tin = 0 ppm). Participants brushed for 1 minute twice daily with their assigned dentifrice and a standard manual toothbrush. The primary clinical endpoint was number of gingival bleeding sites. In vitro analyses characterized tin uptake into biofilm and bacterial glycolysis. **Results:** Of 120 participants randomized to treatment, 115 completed the study. Baseline mean number of bleeding sites (SD) was 35.11 (17.479). At 1 and 3 months, respectively, the mean was 19.52 and 16.64 for the positive control, 26.91 and 21.71 for Experimental dentifrice A, 31.01 and 27.59 for Experimental dentifrice B, and 33.20 and 29.59 for the negative control. At 1 and 3 months, the positive control showed significantly fewer bleeding sites versus all treatments ($P \leq 0.04$) and Experimental dentifrice A had significantly less bleeding versus the negative control ($P \leq 0.041$). Experimental dentifrice B was not significantly different from the negative control ($P \geq 0.438$) at either timepoint. Tin biofilm uptake and in vitro PGRM exhibited a similar trend. (*Am J Dent* 2025;38:155-160).

Clinical significance: SnF_2 dentifrice formulation chemistry influences the level of antigingivitis efficacy, which was also reflected in tin bioavailability, tin uptake into biofilm, and bacterial glycolysis inhibition.

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Introduction

Gingivitis continues to be a prevalent condition globally.[1] While gingivitis is a reversible, early stage of periodontal disease, it can develop into irreversible periodontitis if left untreated.[2] Curtailing this extensive oral health threat requires consistent plaque biofilm removal and prevention.

A critical aspect of plaque control is patient engagement in their daily oral hygiene routine,[3-5] which includes choosing an evidence-based stannous fluoride dentifrice to prevent plaque regrowth between tooth brushings.[6] A recent meta-analysis of 18 randomized clinical trials involving 2,890 subjects[7] demonstrated that gluconate-chelated SnF_2-containing toothpastes reduce gingival bleeding by 51% relative to toothpastes containing sodium fluoride or sodium monofluorophosphate (SMFP) when used for periods up to 3 months.

Recent publications[8,9] have reported that SnF_2 dentifrice formulations manufactured to contain identical 0.454% levels of SnF_2 deliver differential clinical outcomes in randomized controlled clinical trials. These observations support interrogation into how products formulated with the same level of active ingredient (0.454% SnF_2) can deliver differentiated clinical efficacy. SnF_2 must be stabilized (i.e., protected from oxidation, conversion to other non-bioactive or insoluble species, and from hydrolysis) during processing, storage, and delivery to maximize its bioavailability to the oral cavity and biofilm, which is necessary for its therapeutic efficacy. Important considerations in the formulation of bioavailable SnF_2 dentifrice formulations include compatibility with abrasive system, pH of the formulation, and chelation chemistry of SnF_2.

The development of high bioavailable SnF_2 dentifrices in the 1990s was predicated on: (1) provision of sacrificial stannous salts as "antioxidants" reacting with available oxygen to leave SnF_2 protected; (2) the addition of stannous salts to formulations to provide a reservoir resource for stannous delivery over time; and (3) the addition of chelating (metal binding) agents in formulations protecting SnF_2 complexes from hydrolysis and oxidation.[10,11] These formulation principles have been shown to greatly increase the concentration of bioavailable tin reservoir in SnF_2 dentifrice formulations which likely impacts both delivery and efficacy.[11] Based on the principles, the experimental dentifrices were formulated without a chelating agent and at different pH levels, since it is known that under certain conditions, formulations with a lower pH can help prevent SnF_2 hydrolysis.[7]

This clinical trial evaluated the effects of such SnF_2 dentifrice formulation chemistry on antigingivitis efficacy of two experimental 0.454% SnF_2 dentifrices formulated to have low tin bioavailability relative to positive and negative controls after 1 and 3 months of use. Additionally, experimental and control toothpastes were characterized by in vitro assessments of tin uptake into biofilm and inhibition of bacterial glycolysis as assessed by acidogenicity of plaque samples.[12] A previous study[12] has shown consistent results between in vitro assay and clinical study, warranting investigation into these methods as tools to screen dentifrice formulations for relevant activity.

Materials and Methods

This research program consisted of a randomized, four-treatment, parallel-group, double blind clinical trial spanning 3 months plus two in vitro assays that characterized the relative solubility and activity of the study products. All studies evaluated two experimental 0.454% SnF_2 toothpastes formulated to have low tin bioavailability (Experimental dentifrice A,[a] pH 4.7, soluble tin = 592 ppm and Experimental dentifrice B,[a] pH 5.8, soluble tin = 102 ppm) relative to a marketed 0.454% SnF_2 toothpaste (positive control; Crest Pro-Health Sensitive and Enamel Shield,[a] soluble tin = 2,037 ppm) and a marketed 0.76% SMFP toothpaste (negative-control; Colgate Cavity Protection,[b] soluble tin = 0 ppm). The level of soluble tin was confirmed as follows: a toothpaste slurry in degassed water was stirred for 30 minutes in a nitrogen glove box, followed by centrifugation for 20 minutes; the supernatant was diluted and analyzed by inductively coupled plasma–mass spectrometry with matrix-matched calibration standards.

Randomized controlled trial - The objective of the clinical trial was to evaluate two experimental dentifrices relative to positive and negative control toothpastes with respect to gingivitis effects. The study was conducted by Silverstone Research Group in Las Vegas, NV from November 2021 to February 2022 according to the standards of the US Code of Federal Regulations and in accordance with the standard operating procedures of Procter & Gamble. All participants provided written informed consent. Advarra Institutional Review Board approved the study protocol (Pro00061358; NCT06659471).

Clinical assessments - At prescreening, baseline, 1 month, and 3 months, gingivitis was evaluated according to the Löe-Silness Gingivitis Index[13] (LSGI), with scores of 0 to 3 (corresponding to a range from "normal" to "severe inflammation") assigned to each of six areas per scored tooth (distobuccal, buccal, mesiobuccal, mesiolingual, lingual, and distolingual). The same experienced, blinded examiner[14] performed all assessments. All teeth except third molars were assessed. The percentage of bleeding sites was calculated as follows: [(total bleeding sites/number of gradable sites) × 100].

Participants - Participants in the clinical trial were recruited by Silverstone Research Group. The site enrolled healthy adults with baseline gingivitis (10%-70% bleeding sites) and at least 20 scorable teeth. To be included, participants were required to refrain from all non-study oral hygiene products (with the exception of regular flossers, who were permitted to continue flossing) and from all elective dentistry for the duration of the study. Additionally, participation required abstinence from antibiotic, anti-inflammatory, or anticoagulant medication for 4 weeks prior to the baseline visit. Prospective participants were excluded if they had diseases or conditions that might have interfered with study procedures (e.g., widespread caries, tumors of the oral cavity, or advanced periodontal disease), hypersensitivity to the test products, removable oral appliances or fixed orthodontic appliances. Pregnant or lactating participants were likewise excluded. Participants agreed to refrain from all at-home oral hygiene procedures on the mornings of the baseline visit, the 1-month visit, and the 3-month visit.

Experimental design - At the baseline visit, participants gave written informed consent, provided demographic and medical history information, and received an oral examination followed by a gingivitis evaluation. Qualifying participants were enrolled and randomly assigned 1:1:1:1 to one of four treatment groups (negative control, positive control, Experimental dentifrice A, and Experimental dentifrice B), stratified with respect to baseline LSGI score (≤ 1.34 or > 1.34; cut-offs determined on the basis of prior study data, baseline number of bleeding sites (≤ 53, > 53 and ≤ 80, or > 80), sex (male or female), and age (≤ 40 or > 40 years). Participants who met inclusion criteria were randomly assigned to treatment groups with an encoded balance-and-assignment program supplied by the study sponsor. All participants were assigned to use an Oral-B Indicator[a] soft toothbrush for the duration of the study. Then, to maintain blinding of the examiner, each participant moved to a protected area to receive their study products, which were blind-labeled and packaged in similar kit boxes. Participants were provided verbal and written instructions to brush twice daily with their study products, applying enough toothpaste to cover the length of the brush head and brushing for 1 minute (a timer was provided in each kit box for this purpose). After receiving instruction, participants performed the first usage of their study products under supervision at the study site.

At the 1-month and 3-month visits, participants received oral examinations for safety and gingivitis assessments as conducted at the baseline visit, and continuance criteria were assessed.

Statistical analysis - Power analyses were performed with a two-sided test ($\alpha = 0.05$). Twenty-eight participants per group (112 total) were expected to provide $\geq 80\%$ power to detect a between-group difference in the number of bleeding sites of at least 12 bleeding sites, a between-group difference in the mean LSGI score of at least 0.10 units, and a between-group difference in the mean percentage of bleeding sites of at least 7.7%, assuming variabilities of 15.5 bleeding sites, 0.13 units, and 10.0%, respectively. Determination of group size was based on data from a previous, similarly designed unpublished study (data on file).

Baseline demographic and clinical data were summarized. Continuous variables were compared between groups by ANOVA, and categorical responses were compared between groups by chi-square or Fisher's exact test.

Between-group comparisons were made with ANCOVA, with baseline as the covariate. All between-group statistical tests were two-sided ($\alpha = 0.05$). Treatment-by-covariate interaction was assessed for significance ($\alpha = 0.10$).

The primary endpoint was the number of gingival bleeding sites. The primary comparison was between the positive and negative control at 3 months to establish model sensitivity and because the positive control was the only treatment with previous clinical evidence of being different from the negative control.[7] A gatekeeper approach was used in the analysis. This method involved clearly identifying primary comparisons before proceeding to secondary comparisons. By prioritizing primary endpoints, the overall type I error rate was controlled while still allowing for the exploration of secondary hypotheses. Secondary comparisons were between each experimental dentifrice and the negative control at 1 and 3 months. The null hypothesis was that the mean number of bleeding sites would

Table 1. Baseline demographics and clinical measurements.

Demographic	Negative control (n= 30)	Positive control (n=3 0)	Experimental dentifrice A (n= 30)	Experimental dentifrice B (n= 30)	Overall (n= 120)	P-value
Age, years						
Mean (SD)	42.43 (13.42)	40.43 (11.36)	40.87 (12.50)	41.33 (15.29)	41.27 (13.08)	0.944[a]
Range	21 - 63	18 - 66	20 - 64	18 - 61	18 - 66	
Race, n (%)						
American Indian or Alaskan Native[b]	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)	0.854[c]
Asian[b]	3 (10)	2 (7)	2 (7)	4 (13)	11 (9)	
Black or African American[b]	5 (17)	4 (13)	7 (23)	3 (10)	19 (16)	
Multiracial[b]	4 (13)	5 (17)	2 (7)	5 (17)	16 (13)	
Native Hawaiian or Other Pacific Islander[b]	4 (13)	2 (7)	1 (3)	1 (3)	8 (7)	
White/Caucasian[b]	14 (47)	17 (57)	17 (57)	17 (57)	65 (54)	
Sex, n (%)						
Female[b]	22 (73)	21 (70)	20 (67)	20 (67)	83 (69)	0.934[d]
Male[b]	8 (27)	9 (30)	10 (33)	10 (33)	37 (31)	
Clinical measurement						
Mean (SD) number of bleeding sites	35.47 (18.550)	34.97 (15.135)	35.30 (20.117)	34.70 (16.597)	35.11 (17.479)	0.998[a]
Mean (SD) LSGI	1.19 (0.149)	1.20 (0.118)	1.19 (0.153)	1.17 (0.141)	1.19 (0.140)	0.881[a]

Abbreviations: SD: standard deviation; LSGI: Löe-Silness Gingivitis Index.
[a] Two-sided ANOVA P-value for the treatment comparison.
[b] The number (percent) of subjects in each category.
[c] Two-sided Fisher's exact test P-value for the treatment comparison.
[d] Two-sided chi-square P-value for the treatment comparison.

Table 2. ANCOVA summary for number of bleeding sites.[a]

Group (n)		Adjusted mean (SE)	Percent reduction from negative control[b]	Treatment comparison Two-sided P-value (95% CI)		
				Positive control	Exp dentifrice A	Exp dentifrice B
Month 1						
Negative control	(28)	33.20 (2.176)	NA	<0.001 (7.57, 19.78)	0.041 (0.26, 12.32)	0.474 (-3.85, 8.22)
Positive control	(28)	19.52 (2.176)	41.2%	NA	0.017 (-13.42, -1.35)	<0.001 (-17.53, -5.45)
Exp dentifrice A	(29)	26.91 (2.129)	18.9%	NA	NA	0.176 (-10.07, 1.87)
Exp dentifrice B	(29)	31.01 (2.130)	6.6%	NA	NA	NA
Month 3						
Negative control	(26)	29.59 (1.864)	NA	<0.001 (7.91, 17.99)	0.003 (2.83, 12.91)	0.438 (-3.09, 7.08)
Positive control	(30)	16.64 (1.730)	43.8%	NA	0.040 (-9.93, -0.23)	<0.001 (-15.85, -6.06)
Exp dentifrice A	(30)	21.71 (1.729)	26.6%	NA	NA	0.019 (-10.77, -0.98)
Exp dentifrice B	(29)	27.59 (1.761)	6.7%	NA	NA	NA

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; SE: standard error.
[a] ANCOVA model included baseline, treatment, and baseline × treatment as fixed effects.
[b] Percent treatment difference relative to negative control = -100 × (treatment difference/adjusted mean of negative control).

be the same between the positive and negative control groups at 3 months and 1 month (hypotheses 1 and 2, respectively), and between the positive and the experimental groups at 3 months and 1 month (hypotheses 3 and 4, respectively).

In vitro assays - Tin uptake into biofilm - Glass rods (four per test group, N= 16 total for overall experiment) were weighed and then used as substrate for plaque growth. On day 1, rods were inoculated with base medium (3.7% brain heart infusion, 0.25% porcine mucin, 0.1% sodium bicarbonate, 0.1% sucrose, 10 mg/L hemin, and 0.5 mg/L menadione) spiked with 25% fresh human saliva and then incubated in medium for 7 days (37°C, 5% CO_2), with one medium change at day 4. Thirty-minute feedings of 5% sucrose in base medium began on the afternoon of day 7 and were repeated in the morning and afternoon of days 8 through 10. In the morning and afternoon of day 9 and the morning of day 10, the biofilm-supporting rods were treated with a slurry of 16.7% (weight/weight) dentifrice in water for 2 minutes, followed by dipping five times in each of two changes of water to rinse. On the afternoon of day 10, the biofilm-supporting rods were allowed to air dry. Then the glass rod was removed from the tube. Dried biofilm on the glass rod was placed in a 5 mL polypropylene tube. The biofilm was digested with 0.75 mL concentrated nitric acid and 0.75 mL concentrated hydrochloric acid on a hot block at 90°C for 90 minutes. Test solution was prepared by adding appropriate internal standard and diluted the content in the tube to 5 mL with DI water. Then the test solution was analyzed by ICP-MS using matrix matched calibration standards ranging from 1 ng/mL to 1,000 ng/mL Sn in test solution. Measurements on four rods per treatment group were averaged.

Inhibition of plaque glycolysis - Fresh human saliva spiked with Trypticase soy broth[c] was used to initiate plaque growth on glass rods dipped into the medium in a reciprocating motion (four rods per test group,[15] N=16 total for overall experiment). On the third day of growth, each rod was treated with a slurry of 16.7% (weight/weight) dentifrice in water for 2 minutes. This was followed by a water rinse and then immersion into glycolysis medium (0.5% sucrose in TBH, adjusted to pH 6.5)

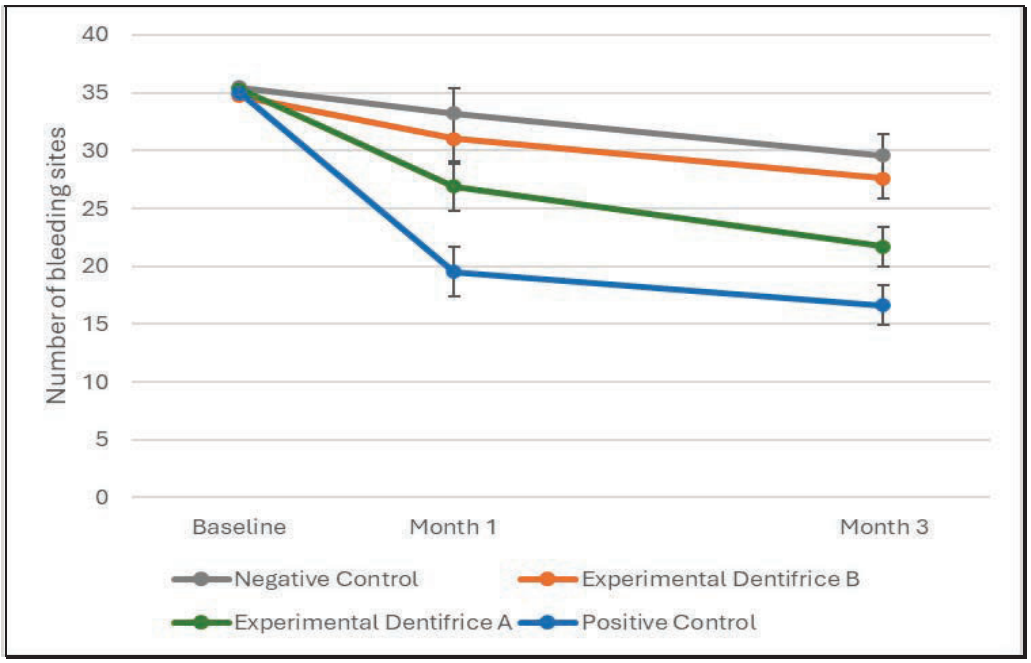

Figure. Number of bleeding sites per group at each timepoint. Error bars represent standard errors. Positive control was statistically significantly different from all other treatments at both time points (P≤ 0.040). Experimental dentifrice A was statistically significantly different versus negative control at 1 and 3 months (P≤ 0.041) and versus Experimental dentifrice B at 3 months (P= 0.019).

Table 3. ANCOVA summary for LSGI.[a]

Group (n)	Adjusted mean (SE)	Percent reduction from negative control[b]	Positive control	Treatment comparison Two-sided P-value (95% CI)	
				Exp dentifrice A	Exp dentifrice B
Month 1					
Negative Control (28)	1.18 (0.019)	NA	<0.001 (0.07, 0.18)	0.037 (0.00, 0.11)	0.246 (-0.02, 0.08)
Positive Control (28)	1.06 (0.019)	10.4%	NA	0.012 (-0.12, -0.02)	<0.001 (-0.14, -0.04)
Exp Dentifrice A (29)	1.13 (0.018)	4.7%	NA	NA	0.343 (-0.08, 0.03)
Exp Dentifrice B (29)	1.15 (0.019)	2.6%	NA	NA	NA
Month 3					
Negative Control (26)	1.14 (0.016)	NA	<0.001 (0.09, 0.17)	0.002 (0.02, 0.11)	0.269 (-0.02, 0.07)
Positive Control (30)	1.01 (0.015)	11.5%	NA	0.003 (-0.11, -0.02)	<0.001 (-0.15, -0.07)
Exp Dentifrice A (30)	1.07 (0.015)	6.0%	NA	NA	0.042 (-0.09, -0.00)
Exp Dentifrice B (29)	1.12 (0.015)	2.1%	NA	NA	NA

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; LSGI: Löe-Silness Gingivitis Index; SE: standard error.
[a] ANCOVA model included baseline, treatment, and baseline × treatment as fixed effects.
[b] Percent treatment difference relative to negative control = -100 × (treatment difference/adjusted mean of negative control).

and incubation at 37°C. Plaque metabolism was monitored with bromocresol purple[d] and chlorophenol red[e] until indicator color change was observed (approximately 6 hours), at which time the pH of the medium was measured. The measurements of four rods per test group were averaged. Delta pH was calculated as change of pH of a treatment from pH of glycolytic media (blank).

Results

Clinical trial - One hundred and twenty adults were enrolled and 115 completed the study. Three subjects voluntarily withdrew from the trial, one subject withdrew due to a protocol violation, and one subject was lost to follow-up. The enrolled population had a mean age of 41.27 years (range, 18-66 years). The percentage of female and male participants was 69% and 31%, respectively. Table 1 shows the baseline demographic and clinical characteristics, which were balanced among the four treatment groups.

Number of bleeding sites (Table 2) - The positive control outperformed all other treatments at both time points (P≤ 0.040). Experimental dentifrice A outperformed the negative control at 1 and 3 months (P≤ 0.041), and outperformed Experimental dentifrice B treatment at 3 months (P=0.019). Experimental dentifrice B was not significantly different from the negative control at either time point (P≥ 0.438). At 3 months, the mean (SE) number of bleeding sites per group was 16.64 (1.730) for the positive control, 21.71 (1.729) for Experimental Dentifrice A, 27.59 (1.761) for Experimental Dentifrice B, and 29.59 (1.864) for the negative control (Figure). These represent reductions from the negative control of 43.8%, 26.6% and 6.7%, respectively.

LSGI Scores (Table 3) - Results for LSGI scores showed the same statistically significant differences across treatment groups as those for number of bleeding sites. The positive control outperformed all other treatments at both time points

Table 4. Tin uptake and iPGRM results.

In vitro assay	Negative control	Positive control	Experimental dentifrice A	Experimental dentifrice B
Tin uptake, μg/mg (SE)	N/A	0.066 A (0.0036)	0.013 B (0.0036)	0.005 B (0.0036)
iPGRM, Δ pH (SE)	1.170 A (0.084)	0.734 B (0.084)	1.135 A (0.084)	0.984 A (0.084)

Abbreviations: iPGRM: in vitro plaque glycolysis regrowth model; SE: pooled standard error from model.
Note: Treatments that are not connected with the same letter are statistically different at the 5% level. Analysis of treatment differences using t-test.

($P \leq 0.012$). Experimental dentifrice A outperformed the negative control at both time points ($P \leq 0.037$) and outperformed Experimental dentifrice B at 3 months ($P = 0.042$). Experimental dentifrice B was not significantly different from the negative control at either time point ($P \geq 0.246$). At 3 months, the mean (SE) LSGI score per group was 1.01 (0.015) for the positive control, 1.07 (0.015) for Experimental dentifrice A, 1.12 (0.015) for Experimental dentifrice B, and 1.14 (0.016) for the negative control. These represent reductions from the negative control of 11.5%, 6.0%, and 2.1%, respectively.

Safety - A total of seven adverse events (AEs) involving seven participants were reported in the study. All AEs were mild and distributed in all treatment groups. There were no AE related drops. The AEs were resolved at the end of the study.

In vitro assays (Table 4) - Tin uptake into biofilm was 0.066 μg/mg for the positive control, 0.013 μg/mg for Experimental dentifrice A, and 0.005 μg/mg for Experimental dentifrice B. Plaque glycolysis was maximally inhibited by the positive control (Δ pH= 0.734) and least inhibited by the negative control (Δ pH= 1.170). For both assays, the positive control was statistically significantly different from all other treatments ($P < 0.05$).

Discussion

The results of the present research show that differences in the formulation chemistry of three 0.454% SnF_2 dentifrices impact their gingivitis reduction efficacy, and the efficacy differences show a similar relationship to results of in vitro measures used to characterize the formulas. The positive control, which is a gluconate-chelated formula designed to stabilize SnF_2 with elevated levels of soluble tin, was associated with increased tin uptake into plaque biofilm and more effective inhibition of plaque glycolysis versus all other treatments. Likewise, the positive control was associated with superior reduction in the number of bleeding sites and LSGI score. Experimental dentifrice A (pH 4.7) performed below the positive control but was better than Experimental dentifrice B (pH 5.8), which showed no statistically significant difference from the negative control with respect to bleeding site reduction or LSGI score reduction. The current results also showed that the antigingivitis efficacy of the experimental formulas and the positive and negative controls demonstrated a consistent rank ordering of products from 1 month through 3 months of use with most effects seen at 1 month. Experimental dentifrice A achieved statistical superiority over Experimental dentifrice B by 3 months. The treatment separation between the four groups provides evidence of the 1-month bleeding model sensitivity.[16]

Formulation-dependent efficacy is linked to the vulnerability of SnF_2 to oxidative breakdown, hydrolysis, or conversion to insoluble or non-bioactive species. There are several formulation strategies that can mitigate loss of SnF_2, including the addition of chelating agents that protect SnF_2 from several losses and breakdowns.[7] Stabilized, bioavailable SnF_2 can penetrate dental plaque, establishing a reservoir from which SnF_2 is steadily released.[17] A salivary concentration sufficient to inhibit bacterial metabolism can thus be maintained for as long as 12 hours.[18] Similarly, stabilized, bioavailable SnF_2 has demonstrated significant persistence in subgingival crevicular fluid for 12 hours after brushing.[19]

This is the first and only study that defines the SnF_2 gingivitis dose response based on bioavailable (soluble) tin concentrations delivered by the SnF_2 product. The study establishes a minimally effective level of soluble and biofilm-delivered tin needed to promote gingivitis efficacy in SnF_2 dentifrices. The current results are consistent with those of previous studies that have shown that the stability and bioavailability of SnF_2, and therefore its antigingivitis efficacy, depend on formulation chemistry.[7] In two independent clinical studies,[8,9] three different commercial formulations of SnF_2 toothpastes were assessed for their ability to reduce the number of bleeding sites over 3 months of use. He et al[8] reported a 3-month randomized controlled clinical trial examining gingivitis and found that three commercially available 0.454% SnF_2 dentifrice products provided statistically significant differentiated reduction of gingival bleeding efficacy over a 3-month period, with the three products reducing bleeding by 84%, 57%, and 28% relative to a negative control. Geisinger et al[9] made a similar observation reporting that three commercially available 0.454% SnF_2 dentifrice products provided statistically significant differentiated reduction of gingival bleeding efficacy over a 3-month period, with the three products reducing bleeding by 28%, 20%, and 18% relative to a negative control. Their relative efficacies were found to be statistically significantly different, despite their identical levels (0.454%) of SnF_2.

Results from the current study demonstrate that formulations containing identical levels of 0.454% SnF_2 can have dramatically differentiated clinical efficacy outcomes likely influenced by the concentration of soluble tin in the formulation and the ability to deliver bioavailable tin into the biofilm. Additional support for this formulation-dependent model of efficacy comes not only from a present study, but also from a study of halitosis, which reported formulation-dependent efficacy in the reduction of volatile sulfur compounds by SnF_2 toothpastes.[20] These volatile sulfur compounds,[21] like gingivitis-associated plaque,[3,22] stem from gram-negative bacteria, making these antihalitosis efficacy results relevant to the understanding of formulation-dependent, SnF_2-based antigingivitis efficacy.

The strengths of the present study include its randomized, double-blind design in accordance with ADA acceptance pro-

gram requirements for chemotherapeutic products for control of gingivitis; employment of an experienced examiner to conduct clinical assessments; similar relationship between clinical and in vitro assessments; and consistent rank ordering of the treatment groups at 1 and 3 months. Presented in vitro models do have some limitations as they do not account for all possible mechanisms that can contribute to disease prevention. Novel methods could be developed in the future to either mimic other mechanisms in vitro or to measure in vivo stannous biofilm delivery and antimicrobial activity. Forthcoming studies could explore new or different SnF_2 technologies for antigingivitis performance, with in vitro assays used as screening tools for efficacy.

This clinical study and the accompanying in vitro characterization of products evaluating three different 0.454% SnF_2 dentifrices and a negative control demonstrated that SnF_2 formulation chemistry resulting in attenuated soluble tin availability negatively impacts clinical gingivitis efficacy. The data supports that concentration of soluble tin in the formula, tin uptake into biofilm, and inhibition of bacterial glycolysis are important parameters related to clinical gingivitis outcomes. The similar trend seen across clinical and in vitro outcomes suggests that the in vitro assays are important to understand the clinical efficacy of SnF_2 dentifrice formulations.

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