Extrinsic Stain Removal Efficacy of a Stannous Fluoride Dentifrice with Sodium Hexametaphosphate

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Abstract

- **Objective:** Two randomized, six-week, double-blind, parallel group, clinical trials were independently conducted to compare the extrinsic stain removal efficacy of a novel whitening therapeutic dentifrice containing 0.454% stannous fluoride and sodium hexametaphosphate in a formulation with high cleaning silica, relative to a positive control whitening dentifrice.

- **Methodology:** Generally healthy adults, 56 for study 1 and 60 for study 2, with visible extrinsic tooth stain were enrolled in the studies. At the baseline visit, stain was assessed on the facial surfaces of the eight central and lateral incisors using the modified Lobene Stain Index. Oral soft and hard tissue examinations were also conducted. In each study, subjects were randomized to either the stannous fluoride + sodium hexametaphosphate toothpaste (Crest® Pro-Health®) or the positive control toothpaste (Colgate® Total® Plus Whitening) to use twice per day for six weeks. Stain and safety were reassessed at weeks three and six.

- **Results:** Fifty-two and 58 subjects completed studies 1 and 2, respectively. In each study, there were no statistically significant differences in Lobene composite stain scores between the two treatment groups across all three visits. Both groups showed statistically significant reductions in Lobene composite stain scores at week three (p < 0.0001) and week six (p < 0.0001) relative to baseline. The percent of Lobene composite scores with a greater than 0.5 unit reduction from baseline at week six was 86% for study 1 and 97% for study 2 for the stannous fluoride + sodium hexametaphosphate dentifrice group.

- **Conclusion:** Collectively, these two stain removal clinical trials demonstrate the statistically significant extrinsic stain removal efficacy for the stannous fluoride + sodium hexametaphosphate dentifrice relative to baseline. There were no statistically significant differences between the stannous fluoride + sodium hexametaphosphate dentifrice and positive control treatment group.

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Introduction

As patient demand for tooth whitening treatments has increased, so has the need for oral care products to sustain the whitening effect. The use of dentifrices formulated with agents to control extrinsic stain is one common approach. Various ingredients have been used in dentifrices for this purpose, including peroxide, abrasives, and chemical agents. Peroxide is a well-established bleaching agent in delivery systems with barriers to promote contact time, but its effectiveness in dentifrices and other barrier-free forms is limited due to brief contact time with the tooth surface and formulation challenges. Abrasives are insoluble ingredients (e.g., silica), commonly used to remove surface stain by physical action. Chemical agents (e.g., pyrophosphates) help maintain whitening due to their strong affinity for tooth minerals. As they are adsorbed to mineral sites, they help desorb pellicle proteins containing stain.

In 2001, sodium hexametaphosphate was introduced in a dentifrice. This chemical whitening agent is in the same class of “calcium phosphate surface active builders” as pyrophosphate, a traditional ingredient used to inhibit surface stain and calculus. Sodium hexametaphosphate is a longer-chain variant, with 10–12 repeating pyrophosphate subunits, so it has a greater affinity for, and retention on the tooth surface compared to pyrophosphate. The polymer chains interact with the stain-trapped pellicle films to lift stain material in the pellicle and prevent the adsorption of new chromogens.

Numerous clinical and technical studies demonstrate the stain removal and prevention properties of sodium hexametaphosphate in dentifrice and chewing gum forms. Gerlach and colleagues reported a 29% reduction in composite stain relative to a negative control after six-weeks’ use of a dentifrice containing 7% sodium hexametaphosphate. Other randomized controlled clinical trials have shown significant stain removal and prevention when subjects used a dentifrice containing sodium hexametaphosphate. Reports in the literature also provide evidence of the agent’s ability to lift and repel surface stains when delivered in chewing gums.

Most recently, sodium hexametaphosphate has been integrated into a high cleaning silica-based dentifrice with 0.454% stabilized stannous fluoride. This antibacterial fluoride provides a unique range of therapeutic benefits relative to other fluoride salts, including protecting against caries, plaque, gingivitis, and dentinal sensitivity. Its use has historically been limited, however, due in part to its potential for extrinsic stain formation.

The objective of these two six-week studies was to assess the stain removal benefit delivered in this novel sodium hexametaphosphate + stannous fluoride dentifrice in subjects with pre-existing natural extrinsic stain. The studies included a positive control whitening dentifrice, which has been shown to significantly reduce extrinsic stain in multiple clinical trials.
Materials and Methods

Study Design
Both clinical trials utilized a six-week, randomized, parallel group, double-blind study design. Study 1 was conducted in West Palm Beach, Florida, USA. Study 2 was carried out in San Antonio, Texas, USA. Both the research protocol and written informed consent were reviewed and approved by an Institutional Review Board prior to study initiation. Generally healthy adults who provided informed consent were screened. Subjects with visible stain on four of the six maxillary anterior teeth, and having at least four of the eight central and lateral incisors with individual Lobene scores > 1.0, were enrolled in the study. Candidates with obvious periodontal disease, sensitivity to tartar control toothpastes, or fixed orthodontics were excluded from participation.

Following baseline assessments of stain and safety, subjects were stratified on baseline stain scores and gender, and then randomized to one of two treatment groups:

- Test dentifrice with 0.454% stannous fluoride + sodium hexametaphosphate in a high cleaning silica base (Crest® Complete-Soft, Procter & Gamble, Cincinnati, OH, USA)
- Positive control whitening dentifrice with 0.243% sodium fluoride, 0.3% triclosan and high-cleaning silica (Colgate® Total® Plus Whitening, Colgate-Palmolive Company, New York, NY)

All test products were packaged in individual kit boxes, each containing two tubes of overtubed or overlabeled test dentifrice, one commercially marketed toothbrush (Crest® Complete-Soft, Procter & Gamble, Cincinnati, OH, USA), and product usage instructions. The boxes were labeled with a unique kit number. Subjects brushed with their assigned product at least twice per day, as they normally would, for six weeks. Subjects brought product kit boxes with them to each visit, and tubes were weighed by site staff to record compliance.

Clinical Evaluations
Stain and safety assessments were conducted at baseline, week three, and week six. The primary efficacy parameter was the modified Lobene Stain Index (Figure 1). The facial surface of each anterior tooth was divided into the gingival region and the body region. The intensity and extent of stain were assessed using 0–3 scales. The Lobene Index was calculated for each body region. The intensity and extent of stain were assessed using 0–3 scales. The Lobene index evaluates extrinsic stain separately in the two studies.

![Figure 1. Lobene Stain Index.](image)

Lobene Stain Index

**Intensity**

0 = No stain
1 = Light stain (yellow to light brown or gray)
2 = Moderate stain (medium brown)
3 = Heavy stain (dark brown to black)

**Area**

0 = No stain detected
1 = Stain covering up to 1/3 of region
2 = Stain covering > 1/3 to 2/3 of region
3 = Stain covering > 2/3 of the region

Statistical Methods
The primary response in this study was the baseline minus post-baseline change in composite (intensity × extent) Lobene scores at three and six weeks after baseline. Separately for each treatment at each visit, the percent of Lobene composite scores with a greater than 0.5 unit reduction from baseline was calculated. Baseline to week three and week six average changes in Lobene scores were tested using paired t-tests. Analysis of covariance (ANCOVA), with treatment as a factor and baseline Lobene score as the covariate, was used to assess treatment differences at both week three and week six. Baseline treatment group comparability was assessed using t-tests (age and stain scores) and Fisher’s Exact Test (% female and % Caucasian). All comparisons were two-sided, using a 5% level of significance.

Results

Study 1
Fifty-six subjects were randomized to treatment and fifty-two completed the study. Subjects ranged in age from 30 to 70 years, with an average age of 49. Fifty-four percent of the subjects were female and 88% were Caucasian. Mean Lobene composite scores were not statistically significantly different (p = 0.43) between groups at baseline (Table I).

### Table I

<table>
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<tr>
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<th>SnF2 + SHMP Dentifrice (n = 28)</th>
<th>Positive Control Dentifrice (n = 28)</th>
<th>Overall (n = 56)</th>
<th>Two-Sided p-values</th>
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<td>Age, Years Mean (SD)</td>
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<td>49.5 (7.44)</td>
<td>48.5 (9.64)</td>
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<td>Sex, N (%) Female</td>
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<td>15 (53.6%)</td>
<td>30 (53.6%)</td>
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<td>0 (0%)</td>
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<tr>
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<td>24 (85.7%)</td>
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<td>Hispanic</td>
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<td>4 (14.3%)</td>
<td>4 (7.1%)</td>
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<td>Stain, Mean (SD)</td>
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<tr>
<td>Composite</td>
<td>2.60 (1.65)</td>
<td>2.50 (1.50)</td>
<td>2.54 (1.57)</td>
<td>0.43*</td>
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</table>

*Two-sided p-value for the treatment comparison from a two sample t-test.

At week three, the Lobene composite adjusted mean was 1.04 for the stannous fluoride dentifrice and 1.08 for the positive control. Change from baseline was 1.50 and 1.46 for the stannous fluoride dentifrice and for the positive control group, respectively. Both treatment groups provided statistically significant (p < 0.0001) stain reductions relative to baseline. There was no statistically significant difference (p = 0.73) between the two groups (Table II).

At week six, the Lobene composite adjusted mean was 0.94 for the stannous fluoride dentifrice and 0.90 for the positive control. Change from baseline was 1.59 for the stannous fluoride dentifrice group and 1.64 for the positive control group. Both treatment groups provided statistically significant (p < 0.0001) stain reductions relative to baseline. There was no statistically significant difference (p = 0.64) between the two groups at week six (Table II).
The percent of Lobene composite scores with a greater than 0.5 unit reduction from baseline at weeks three and six were 82% and 86%, respectively, for the stannous fluoride group, and 78% and 85%, respectively, for the positive control group (Figure 2).

### Study 2

Sixty subjects were randomized to treatment and fifty-eight subjects completed the study. Subjects ranged in age from 29 to 71 years, with an average of 51 years. Sixty-five percent of the subjects were female, 58% were Hispanic, and 32% were Caucasian. The demographic profile of subjects in study 2 was similar to that of study 1, except there were more Hispanic participants in study 2 (Table III). The baseline Lobene composite mean for the stannous fluoride dentifrice group was 3.37. The baseline Lobene composite mean for the positive control group was 3.14. Overall the baseline stain scores were higher in study 2 when compared to study 1. There was no statistically significant difference (p = 0.09) between the two groups at baseline (Table IV).

The week six Lobene composite adjusted mean was 0.22 for the stannous fluoride dentifrice and 0.25 for the positive control group. Change from baseline for the stannous fluoride dentifrice group and the positive control group was 3.05 and 3.02, respectively. There was no statistically significant difference (p = 0.61) between the two groups at week six. The week three Lobene composite adjusted mean was 1.43 for the stannous fluoride dentifrice and 1.51 for the positive control group. The week three Lobene composite adjusted mean change from baseline for the stannous fluoride dentifrice group was 1.84. The week three Lobene composite adjusted mean change from baseline for the positive control group was 1.76. There was no statistically significant difference (p = 0.51) between the two groups at week three (Table IV). At weeks three and six, both treatment groups provided statistically significant (p < 0.0001) stain reduction relative to baseline as measured by the Lobene composite stain index.

The percent of Lobene composite scores with a greater than 0.5 unit reduction from baseline at week six was 97% for the stannous fluoride dentifrice group and 97% for the positive control group. The percent of Lobene composite scores with a greater than 0.5 unit reduction from baseline at week three was 81% for the stannous fluoride dentifrice group and 80% for the positive control group (Figure 3).
showing extrinsic stain removal and inhibition for this new stannous fluoride dentifrice containing sodium hexametaphosphate.18,19 This novel dentifrice technology represents a paradigm shift in stannous fluoride formulations, as it is the first to deliver the efficacy of the antibacterial fluoride with the cosmetic benefits of extrinsic whitening and calculus control. Stannous fluoride was the first clinically proven fluoride agent used in a dentifrice (Crest) in the 1950s.20,21 Upon review of clinical findings, the Council on Dental Therapeutics of the American Dental Association awarded its first dentifrice Seal of Acceptance to Crest with stannous fluoride for the therapeutic prevention of tooth decay.22 The early formulations were effective at caries protection, but there were formulation and stability limitations that prompted a change to other fluorides, such as sodium fluoride.23 In the mid-1990s, researchers discovered new ways to formulate a stable and efficacious stannous fluoride dentifrice that provided its full range of therapeutic benefits: protection from caries; reduction of gingivitis; and control of hypersensitivity.24 The stabilized stannous fluoride product, however, still had limitations, including the potential for extrinsic tooth stain and astringent taste.25

Continued formulation work led to the development of a unique technology combining stannous fluoride and sodium hexametaphosphate, an advanced tartar control and whitening agent, in a high cleaning silica-based dentifrice.15 A low-water or “non-hydrated gel matrix” is used in this patented system to ensure stability of the sodium hexametaphosphate, which is comprised of very small crystals, approximately a few hundred microns in diameter. Sodium hexametaphosphate molecules are highly soluble in water. During brushing, the sodium hexametaphosphate is rapidly dissolved, then reacts chemically to lift stain, leaving a protective coating on the tooth surface to repel new stains.19

Extensive controlled clinical trials have been conducted on the patented technology, marketed as the Polyfluorite System, to show it still delivers all the soft and hard tissue benefits historically associated with stannous fluoride. Randomized trials demonstrate significant reductions in bleeding, gingivitis, and plaque for the stannous fluoride + sodium hexametaphosphate dentifrice relative to a negative control.26,27 These reports support numerous other published studies showing gingival health benefits for stannous fluoride and the novel system.28-32 Two eight-week trials evaluated the desensitizing benefits of the stannous fluoride + sodium hexametaphosphate technology. Both showed reductions in thermal and tactile sensitivity.33,34 The caries benefit of an experimental stannous fluoride + sodium hexametaphosphate dentifrice was also evaluated in a two-year clinical trial by Stookey, et al.35 Evaluable subjects using the stannous fluoride + sodium hexametaphosphate experimental dentifrice for two years experienced 17%–25% (p ≤ 0.02) lower caries increments relative to subjects using the 1100 ppm fluoride control dentifrice. Results for the stannous fluoride + sodium hexametaphosphate group were similar to those for the 2800 ppm fluoride dentifrice.

The number of stannous fluoride + sodium hexametaphosphate showing extrinsic stain removal benefits for the novel stannous fluoride dentifrice at weeks three and six relative to baseline (p < 0.0001) among patients with representative natural stain. These findings support other clinical research showing extrinsic stain removal and inhibition for this new stannous fluoride dentifrice containing sodium hexametaphosphate.18,19 This novel dentifrice technology represents a paradigm shift in stannous fluoride formulations, as it is the first to deliver the efficacy of the antibacterial fluoride with the cosmetic benefits of extrinsic whitening and calculus control. Stannous fluoride was the first clinically proven fluoride agent used in a dentifrice (Crest) in the 1950s.20,21 Upon review of clinical findings, the Council on Dental Therapeutics of the American Dental Association awarded its first dentifrice Seal of Acceptance to Crest with stannous fluoride for the therapeutic prevention of tooth decay.22 The early formulations were effective at caries protection, but there were formulation and stability limitations that prompted a change to other fluorides, such as sodium fluoride.23 In the mid-1990s, researchers discovered new ways to formulate a stable and efficacious stannous fluoride dentifrice that provided its full range of therapeutic benefits: protection from caries; reduction of gingivitis; and control of hypersensitivity.24 The stabilized stannous fluoride product, however, still had limitations, including the potential for extrinsic tooth stain and astringent taste.25

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**Conclusions**

These two six-week double-blind, parallel group studies showed similar extrinsic stain removal benefits for the novel stannous fluoride and sodium hexametaphosphate dentifrice with high cleaning silica (Crest Pro-Health) relative to a positive control whiten-
ing dentifrice (Colgate Total + Whitening). These results, as well as other investigations, support the stain removal efficacy of this novel antibacterial, desensitizing, fluoride dentifrice.

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References