

Study Summary

1. Introduction

Stannous fluoride is a broad spectrum antimicrobial agent that has been used in dentistry as a chemical adjunct to prevent dental caries and gingivitis. The mechanism of action of this agent constitutes inhibition and reduction of bacterial plaque biomass, virulence, and metabolism.

2. Study Objectives

The objective to this study was to compare the efficacy of a stabilized stannous fluoride dentifrice vs. a negative control in the prevention of gingivitis over a 6-month period following an oral prophylaxis.

3. Investigational Plan

3.1 Study Design

This study was a randomized, stratified, single center, double-blind, parallel group, clinical trial. A sufficient number of qualified subjects were entered into the study so that 120 (60 per cell) could be reasonably expected to complete the study. During the treatment phase, subjects used the investigational dentifrice, or control, twice daily, as instructed, for 6 months. Subjects were supplied with the dentifrice and toothbrush at each study visit. Efficacy measurements were obtained at baseline, 3-months, and 6-months, post treatment. Anti-gingivitis efficacy was determined using mean Modified Gingival Index and Gingival Bleeding Index scores while anti-plaque efficacy was measured using mean Plaque Index scores. Oral soft tissue (OST) and oral hard tissue exams were conducted at each examination interval to monitor oral safety.

3.2 Selection of Study Population

3.2.1 Inclusion Criteria

Subjects were considered eligible for enrollment into this study if they:

- a. had provided written Informed Consent;
- b. had been adult males and females between 18 and 65 years of age with good general health;
- c. had a minimum of 18 natural teeth with facial and lingual scorable surfaces. Teeth that were grossly carious, fully crowned, or extensively restored were not included; and
- d. had a baseline MGI score of at least 1.75 and not greater than 2.3, and a Turesky Plaque score of at least 1.5.

3.2.1.1 Continuance Criteria

After study enrollment, each subject may have had their visit rescheduled or may have been discontinued from the study and/or excluded from the efficacy analyses where there was evidence of:

- use of any dentifrices or mouthrinses other than those assigned.

3.2.2 Exclusion Criteria

Subjects were excluded from the study if they:

- a. had widespread caries or chronic neglect;
- b. had antibiotic, anti-inflammatory or anti-coagulant therapy for 30 days prior to the baseline exam;
- c. had medical conditions that the Investigator considered significant and that may have compromised the evaluation of study results;
- d. were currently participating in any other clinical trial;
- e. had participated in a clinical trial for plaque/gingivitis within the previous 30 days;
- f. were pregnant or lactating;
- g. had orthodontic appliances or removable partial dentures;
- h. had soft or hard tissue tumor of the oral cavity;
- i. had advanced periodontal disease;
- j. had known hypersensitivity to stannous fluoride;
- k. had known sensitivity to tartar control dentifrices;
- l. had history of hepatitis, diabetes, or other communicable diseases;
- m. had history of rheumatic fever, heart murmur, mitral valve prolapse or other conditions requiring prophylactic antibiotic coverage prior to invasive dental procedures;
- n. had history of significant adverse effects following the use of oral hygiene products such as toothpaste and mouthrinse;
- o. had oral prophylaxis during the course of the study. They may have received dental treatment, but no dental cleaning; or
- p. had oral pathoses that could have interfered with compliance and/or examinations or that needed treatment.

3.3 Removal of Subjects from the Study

Subjects may have withdrawn from the study at any time or for any reason. The Investigator documented the cause for withdrawal for any discontinued subjects. The Investigator may have removed subjects from the study at any time. Subjects being withdrawn for medical reasons were referred to a physician/dentist by the study personnel and had their condition monitored to resolution or until deemed clinically not significant.

3.4 Study Procedures

At baseline visit, subjects received OST, Hard Tissue, Gingival (MGI), Bleeding, and Plaque (PI) exams. Following the baseline examinations, subjects received an oral prophylaxis and were randomly assigned to a treatment group. Product was dispensed and subjects were given verbal and written instructions on product usage. The dentifrice was supplied in identical white tubes. Subjects were instructed to brush twice daily for 1 minute, using the same method they normally did. At 3 months and 6 months, post treatment, subjects received MGI, Bleeding site, and PI exams to reevaluate all baseline parameters, in addition to OST and Hard Tissue exams.

3.4.1 Efficacy Assessments

Efficacy was assessed by MGI scores, Bleeding sites, and plaque scores at each post-treatment exam visit.

3.4.2 Safety Assessments

Safety evaluations included assessment of the oral soft tissue, oral hard tissues including teeth and restorations.

3.5 Treatments

3.5.1 Identity of Investigational Products

- Experimental dentifrice: 0.454% Stabilized Stannous fluoride dentifrice
- Negative control dentifrice: 0.76% Sodium monofluorophosphate dentifrice

3.5.2 Blinding

Subjects and site personnel were blinded as to treatment assignment. To preserve the blinding, investigational products and kits were identical in their appearance. The dentifrice tubes were either packaged in white foil or foiless laminate tubes or were provided in original primary commercial packaging and overtubed by the Sponsor for blinding purpose.

3.6 Statistical Methods

3.6.1 Statistical Analysis Plans

Statistical analysis was based on whole-mouth average MGI scores, plaque scores, and the numbers of bleeding sites observed. For each of these variables, an analysis of covariance (ANCOVA) was performed on the change from baseline, with the baseline score as the covariate. Separate analyses were performed for 3-month and 6-month data, with the 6-

month data of primary interest. In addition, percent difference based on change from baseline was calculated.

3.6.1.1 Demographic and Baseline Characteristics

Demographic and Baseline data were summarized by treatment group to assess baseline comparability.

4. Results

Of the 143 subjects enrolled in the study, 133 were available for the 3-month examination and 130 subjects completed the entire 6-month study. Subjects who did not complete the study did so for reasons unrelated to the use of either of the two dentifrices. Demographic characteristics for baseline, 3- and 6-month results are shown in Tables 1-3. Subjects in the experimental dentifrice and negative control groups were equally represented in terms of age and gender throughout the trial.

A summary of the 3-month Modified Gingival Index (MGI) data is reported in Table 4. The average baseline MGI scores were 2.03 for the experimental group and 2.04 for the negative control group. The 3-month MGI scores were analyzed using an ANCOVA with baseline MGI score as the covariate. The adjusted mean 3-month MGI scores were 1.75 for the experimental dentifrice and 1.98 for the negative control dentifrice. The difference between groups was statistically significant ($p < 0.001$).

A summary of the 3-month gingival bleeding data is reported in Table 5. The average number of gingival bleeding scores at baseline was 9.36 for the experimental group and 8.67 for the negative control group. The analyses of covariance used the number of bleeding scores at baseline as the covariate. The adjusted mean 3-month bleeding scores were 4.14 for the experimental dentifrice and 7.92 for the negative control dentifrice. The difference between groups was statistically significant ($p < 0.001$).

A summary of the 3-month plaque data is reported in Table 6. The mean plaque score at baseline was 2.74 for the experimental group and 2.90 for the negative control group. The analyses of covariance used the baseline plaque scores as the covariate. The adjusted mean 3-month plaque scores were 2.24 for the experimental dentifrice and 2.38 for the negative control dentifrice and the difference approached statistical significance ($p = 0.06$).

For subjects with MGI scores at 6 months (Table 7), the average baseline MGI scores were 2.03 for the experimental group and 2.04 for the negative control group. The 6-month MGI scores were analyzed using the same analysis of covariance methods used for the 3-month MGI scores. The adjusted mean 6-month MGI scores were 1.57 for the experimental dentifrice and 2.01 for the negative control dentifrice. The difference between groups was statistically significant ($p < 0.001$).

For subjects who were examined at 6 months (Table 8), the average number of gingival bleeding scores at baseline was 9.39 for the experimental group and 8.68 for the negative control group. The adjusted mean 6-month bleeding scores were 3.81 for the experimental dentifrice and 8.88 for the negative control dentifrice and the difference between groups was again statistically significant ($p < 0.001$).

For subjects examined at 6 months, the mean plaque score at baseline was 2.73 for the experimental group and 2.91 for the negative control group (Table 9). The adjusted mean 6-month plaque scores were 2.14 for the experimental group and 2.30 for the negative control group and this difference was statistically significant ($p=0.01$).

Examinations of the oral tissues after three and six months revealed no remarkable findings related to either of the test dentifrices.

5. Discussion and Conclusions

The results of the present clinical study demonstrate that use of the experimental stannous fluoride dentifrice over a 6 month period provides a statistically significant effect in the control and prevention of gingivitis and reduction in dental plaque as compared to a negative control dentifrice.

**EOT TABLE 1
DEMOGRAPHIC CHARACTERISTICS**

SUBJECTS WITH BASELINE DATA

DEMOGRAPHIC CHARACTERISTICS	0.454% SNF2 (n=71)	NEGATIVE CONTROL (n=72)	TOTAL (n=143)
AGE (YEARS)			
Mean	36.6	37.8	37.2
SD	10.49	11.27	10.87
Minimum	18.0	18.0	18.0
Maximum	65.0	64.0	65.0
SEX^a			
Female	47 (66.2%)	48 (66.7%)	95 (66.4%)
Male	24 (33.8%)	24 (33.3%)	48 (33.6%)
RACE^a			
White	51 (71.8%)	50 (69.4%)	101 (70.6%)
Hispanic	12 (16.9%)	12 (16.7%)	24 (16.8%)
Asian	1 (1.4%)	2 (2.8%)	3 (2.1%)
African American	7 (9.9%)	8 (11.1%)	15 (10.5%)
SMOKER^a			
Yes	19 (26.8%)	18 (25.0%)	37 (25.9%)
No	52 (73.2%)	54 (75.0%)	106 (74.1%)
^a Number and percent of subjects in each category.			

**EOT TABLE 2
DEMOGRAPHIC CHARACTERISTICS**

SUBJECTS WITH 3-MONTH DATA

DEMOGRAPHIC CHARACTERISTICS	0.454% SNF2 (n=66)	NEGATIVE CONTROL (n=67)	TOTAL (n=133)
AGE (YEARS)			
Mean	37.1	38.3	37.7
SD	10.70	11.29	10.98
Minimum	18.0	18.0	18.0
Maximum	65.0	64.0	65.0
SEX^a			
Female n (%)	45 (68.2%)	44 (65.7%)	89 (66.9%)
Male n (%)	21 (31.8%)	23 (34.3%)	44 (33.1%)
RACE^a			
White	48 (72.7%)	46 (68.7%)	94 (70.7%)
Hispanic	11 (16.7%)	11 (16.4%)	22 (16.5%)
Asian	1 (1.5%)	2 (3.0%)	3 (2.3%)
African American	6 (9.1%)	8 (11.9%)	14 (10.5%)
SMOKER^a			
Yes	16 (24.2%)	15 (22.4%)	31 (23.3%)
No	50 (75.8%)	52 (77.6%)	102 (76.7%)
^a Number and percent of subjects in each category.			

**EOT TABLE 3
DEMOGRAPHIC CHARACTERISTICS**

SUBJECTS WITH 6-MONTH DATA

DEMOGRAPHIC CHARACTERISTICS	0.454% SNF2 (n=64)	NEGATIVE CONTROL (n=66)	TOTAL (n=130)
AGE (YEARS)			
Mean	37.1	38.5	37.8
SD	10.86	11.31	10.07
Minimum	18.0	18.0	18.0
Maximum	65.0	64.0	65.0
SEX^a			
Female	44 (68.8%)	43 (65.2%)	87 (66.9%)
Male	20 (31.2%)	23 (34.8%)	43 (33.1%)
RACE^a			
White	47 (73.4%)	46 (69.7%)	93 (71.5%)
Hispanic	11 (17.2%)	11 (16.7%)	22 (16.9%)
Asian	1 (1.6%)	2 (3.0%)	3 (2.3%)
African American	5 (7.8%)	7 (10.6%)	12 (9.2%)
SMOKER^a			
Yes	15 (23.4%)	15 (22.7%)	30 (23.1%)
No	49 (76.6%)	51 (77.3%)	100 (76.9%)
^a Number and percent of subjects in each category.			

**EOT TABLE 4
3-MONTH ANALYSIS RESULTS FOR GI SCORES**

MODIFIED GINGIVAL INDEX

TREATMENT GROUP	BASELINE SCORES		
	<u>N</u>	<u>MEAN</u>	<u>SD</u>
0.454% SnF2	66	2.03	0.095
Negative control	67	2.04	0.099
ANOVA <i>p</i>-value for treatment groups at baseline = 0.435			
TREATMENT GROUP	12-WEEK SCORES		
	<u>N</u>	<u>MEAN^a</u>	<u>% REDUCTION^b</u>
0.454% SnF2	66	1.75	11.5%
Negative control	67	1.98	N/A
ANCOVA MSE = 0.018			
TREATMENT COMPARISON		TREATMENT COMPARISON <i>p</i> -VALUE	
0.454% SnF2 vs. Negative control		<0.001	
^a 3-month means are adjusted means from analysis of covariance (ANCOVA). ^b % Reduction = 100% (Negative control mean minus 0.454% SnF2 mean) divided by Negative control mean.			

**EOT TABLE 5
3-MONTH ANALYSIS RESULTS FOR BLEEDING SCORES**

TREATMENT GROUP	BASELINE SCORES		
	<u>N</u>	<u>MEAN</u>	<u>SD</u>
0.454% SnF2	66	9.36	3.185
Negative control	67	8.67	3.377
ANOVA <i>p</i>-value for treatment groups at baseline = 0.226			
TREATMENT GROUP	3-MONTH SCORES		
	<u>N</u>	<u>MEAN^a</u>	<u>% REDUCTION^b</u>
0.454% SnF2	66	4.14	47.7%
Negative control	67	7.92	N/A
ANCOVA MSE = 7.629			
TREATMENT COMPARISON		TREATMENT COMPARISON <i>p</i> -VALUE	
0.454% SnF2 vs. Negative control		<0.001	
^a 3-month means are adjusted means from analysis of covariance (ANCOVA). ^b % Reduction = 100% (Negative control mean minus 0.454% SnF2 mean) divided by Negative control mean.			

EOT TABLE 6
3-MONTH ANALYSIS RESULTS FOR PLAQUE SCORES
TURESKY MODIFICATION OF THE QUIGLEY-HEIN PLAQUE INDEX

TREATMENT GROUP	BASELINE SCORES		
	<u>N</u>	<u>MEAN</u>	<u>SD</u>
0.454% SnF2	66	2.74	0.412
Negative control	67	2.90	0.355
ANOVA <i>p</i>-value for treatment groups at baseline = 0.020			
TREATMENT GROUP	3-MONTH SCORES		
	<u>N</u>	<u>MEAN^a</u>	<u>% REDUCTION^b</u>
0.454% SnF2	66	2.24	5.6%
Negative control	67	2.38	N/A
ANCOVA MSE = 0.158			
TREATMENT COMPARISON		TREATMENT COMPARISON <i>p</i> -VALUE	
0.454% SnF2 vs. Negative control		0.060	
^a 3-month means are adjusted means from analysis of covariance (ANCOVA). ^b % Reduction = 100% (Negative control mean minus 0.454% SnF2 mean) divided by Negative control mean.			

**EOT TABLE 7
6-MONTH ANALYSIS RESULTS FOR GI SCORES**

MODIFIED GINGIVAL INDEX

TREATMENT GROUP	BASELINE SCORES		
	<u>N</u>	<u>MEAN</u>	<u>SD</u>
0.454% SnF2	64	2.03	0.096
Negative control	66	2.04	0.099
ANOVA <i>p</i>-value for treatment groups at baseline = 0.376			
TREATMENT GROUP	6-MONTH SCORES		
	<u>N</u>	<u>MEAN^a</u>	<u>% REDUCTION^b</u>
0.454% SnF2	64	1.57	21.7%
Negative control	66	2.01	N/A
ANCOVA MSE = 0.042			
TREATMENT COMPARISON		TREATMENT COMPARISON <i>p</i> -VALUE	
0.454% SnF2 vs. Negative control		<0.001	
^a 6-month means are adjusted means from analysis of covariance (ANCOVA). ^b % Reduction = 100% (Negative control mean minus 0.454% SnF2 mean) divided by Negative control mean.			

**EOT TABLE 8
6-MONTH ANALYSIS RESULTS FOR BLEEDING SCORES**

TREATMENT GROUP	BASELINE SCORES		
	<u>N</u>	<u>MEAN</u>	<u>SD</u>
0.454% SnF2	64	9.39	3.220
Negative control	66	8.68	3.402
ANOVA <i>p</i>-value for treatment groups at baseline = 0.225			
TREATMENT GROUP	6-MONTH SCORES		
	<u>N</u>	<u>MEAN^a</u>	<u>% REDUCTION^b</u>
0.454% SnF2	64	3.81	57.1%
Negative control	66	8.88	N/A
ANCOVA MSE = 10.120			
TREATMENT COMPARISON		TREATMENT COMPARISON <i>p</i> -VALUE	
0.454% SnF2 versus Negative control		<0.001	
^a 6-month means are adjusted means from analysis of covariance (ANCOVA). ^b % Reduction = 100% (Negative control mean minus 0.454% SnF2 mean) divided by Negative control mean.			

EOT TABLE 9
6-MONTH ANALYSIS RESULTS FOR PLAQUE SCORES
TURESKY MODIFICATION OF THE QUIGLEY-HEIN PLAQUE INDEX

TREATMENT GROUP	BASELINE SCORES		
	<u>N</u>	<u>MEAN</u>	<u>SD</u>
0.454% SnF2	64	2.73	0.414
Negative control	66	2.91	0.347
ANOVA <i>p</i>-value for treatment groups at baseline = 0.009			
TREATMENT GROUP	6-MONTH SCORES		
	<u>N</u>	<u>MEAN^a</u>	<u>% REDUCTION^b</u>
0.454% SnF2	64	2.14	6.9%
Negative control	66	2.30	N/A
ANCOVA MSE = 0.124			
TREATMENT COMPARISON		TREATMENT COMPARISON <i>p</i> -VALUE	
0.454% SnF2 vs. Negative control		0.014	
^a 6-month means are adjusted means from analysis of covariance (ANCOVA). ^b % Reduction = 100% (Negative control mean minus 0.454% SnF2 mean) divided by Negative control mean.			