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TITLE: **Determination of the Antiplaque/Antigingivitis Efficacy of Essential Oil-Containing Mouthrinses using an Experimental Gingivitis Model**

Protocol Number: **931-1309**

Research Report Number: **931-1151**

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Sponsor: **Pfizer Consumer Healthcare R&D**
Pfizer Inc
Oral Care

Study Initiation Date: **September 6, 2000**

Study Completion Date: **September 30, 2000**

Date of Report: **January 16, 2002**

This study was performed in compliance with Good Clinical Practice (GCP) Guidelines.

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Synopsis

TITLE: Determination of the Antiplaque/Antigingivitis Efficacy of Essential Oil-Containing Mouthrinses using an Experimental Gingivitis Model (Study No. 931-1309)

INVESTIGATORS: Suru Mankodi, D.D.S.

STUDY CENTER: Dental Products Testing Inc, 1497 Forest Hill Blvd.
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STUDY PERIOD: First Enrollment: September 6, 2000
Last Completed: September 30, 2000

OBJECTIVES: The objective of this two-week controlled clinical trial was to compare the antiplaque/antigingivitis efficacy of two essential oil-containing mouthrinse formulations containing the identical fixed combination of four essential oils.

PURPOSE AND METHODS: This was a randomized, examiner-blind, parallel group, two-week controlled clinical trial. This experimental gingivitis model has been successfully used in the past as a short-term model to evaluate the chemotherapeutic efficacy of mouthrinses in reducing gingival inflammation, bleeding, and dental plaque. Healthy subjects with slight to moderate gingival inflammation and dental plaque were enrolled and instructed to rinse with 20 ml twice daily, for 30 seconds, for two weeks with one of the following: an essential oil-containing rinse with 0.02% sodium fluoride (EOF), an essential oil-containing mouthrinse without fluoride (EO) or a negative control (5% hydroalcohol).

Antiplaque/antigingivitis efficacy was determined by evaluation of the amount of supragingival dental plaque and of visual signs of marginal gingivitis, and secondarily by gingival bleeding determinations.

The two daily rinses Monday through Friday were supervised and separated by at least four hours. Subjects were instructed to follow their usual dietary habits but to refrain from using any oral care products other than the provided mouthrinse. The use of chewing gums and mints for the duration of the study was discouraged. Subjects were also instructed to stop normal oral hygiene such as brushing and flossing throughout the study period.

NUMBER OF SUBJECTS: Of the 216 subjects entered into the study, 200 subjects were evaluable at two weeks.

The planned sample size of 195 (65 per treatment group) completed, evaluable subjects was based on estimates of variability and adjusted means from similarly designed Pfizer Consumer Healthcare studies. The sample size provides greater than 80% probability that the upper 95% confidence limit for the difference between means for EOF rinse and EO rinse is less than 10% of the EO rinse mean. This assumes an underlying mean no more than 2.5% higher for EOF rinse than for EO rinse, and coefficients of variation (c.v.) of 14% for mean Modified Gingival

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Index and 15% for mean Plaque Index.

MAIN CRITERIA FOR INCLUSION: Generally healthy subjects with slight to moderate gingival inflammation ($MGI \geq 1.95$) and dental plaque ($PI \geq 1.95$), aged 18-65, with at least 20 scorable natural teeth, and not on antibiotic or anti-inflammatory medication were entered into the study.

TEST PRODUCTS, DOSE, ADMINISTRATION AND DURATION OF TREATMENT: Subjects were instructed to rinse with 20 ml twice daily, for 30 seconds, for two weeks with one of the following: EOF rinse, EO rinse or the negative control rinse.

CRITERIA FOR EVALUATION: Gingival inflammation was assessed using both non-invasive (Modified Gingival Index) and invasive measurements (Bleeding Index). Presence of disclosed dental plaque was evaluated using the well-established Turesky Modification of the Quigley-Hein Plaque Index.

Efficacy: Antiplaque/antigingivitis efficacy was determined primarily by evaluation of the levels of supragingival dental plaque and of visual signs of marginal gingivitis, and secondarily by gingival bleeding determinations. Gingivitis and plaque levels were examined at the initiation and conclusion of the two-week study.

The primary efficacy variables were: mean Modified Gingival Index (MGI) and mean Plaque Index (PI) at two weeks. The secondary efficacy variable was: mean Gingival Bleeding Index (BI) at two weeks.

Safety: Adverse events were reported by the subjects during weekday visits for supervised rinsing and at the clinical examinations.

STATISTICAL METHODS: For each of the primary and secondary efficacy variables, between-treatment differences after two weeks of treatment were tested by a one-way analysis of covariance model with treatment as a factor and the corresponding baseline value as the covariate. The treatment-by-baseline interaction was tested at the 0.05 level to assess heterogeneity of slopes. The treatment groups were compared with respect to age and baseline efficacy variables by a one-way ANOVA with treatment as a factor, with respect to race by means of Fisher's Exact test, and with respect to other demographic variables by means of a chi-square test.

The following efficacy comparisons were performed for each primary and secondary efficacy parameter:

- a) EO rinse (positive control) versus 5% hydroalcohol mouthrinse (negative control)
- b) EOF rinse versus 5% hydroalcohol control mouthrinse
- c) EOF rinse versus EO rinse

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The comparative criteria established to demonstrate acceptable performance for the test product EOF rinse were twofold:

- a) The test product had to be statistically significantly superior to the 5% hydroalcohol control for each of the primary efficacy variables based on a two-sided test;
- b) The test product had to be "at least as good as" the positive control. This latter criterion was met for the test product if, for each of the primary efficacy variables, the upper limit of the one-sided 97.5% confidence interval for the difference between the means for the test and the positive control (expressed as a percentage difference relative to positive control) was below 10%.

The study was considered valid if the post-treatment means of the primary efficacy variables for the positive control were statistically significantly lower than the corresponding means of the negative control based on a two-sided test.

SUMMARY/CONCLUSION:

Efficacy Results: In this two week no oral hygiene model, the EOF rinse was: a) efficacious in reducing gingival inflammation with concomitant antiplaque efficacy by a statistically significant greater reduction in gingival inflammation and plaque than the negative control, and b) "at least as good as" the positive control (EO mouthrinse) in inhibition of gingival inflammation and plaque in this two week no oral hygiene model.

Mean Modified Gingival Index and Mean Plaque Index (Primary Efficacy Variables)

The EOF rinse exhibited statistically significantly lower mean Modified Gingival Index and mean Plaque Index (Tables below) than the negative control after two weeks of treatment ($p < 0.001$). The percentage reductions in means were 12.3% and 30.0%, respectively relative to the negative control.

The mean Modified Gingival Index and mean Plaque Index at two weeks for EO rinse (the positive control) were statistically significantly lower than the corresponding means of the negative control ($p < 0.001$). The percentage reductions were 14.8% and 28.4%, relative to the negative control, respectively.

For both the EOF rinse and the positive control, mean MGI and mean PI were statistically significantly lower after two weeks of treatment than at baseline ($p \leq 0.002$). For the negative control group, there was little change in mean MGI after two weeks of treatment but there was a statistically significant increase in mean PI from the baseline ($p < 0.001$).

Bleeding Index (Secondary Efficacy Variable)

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Means at two weeks were statistically significantly lower for both the EOF rinse and the positive control compared with the negative control ($p < 0.001$; see table below). For both the EOF rinse and the positive control, the mean BI was statistically significantly lower after two weeks of treatment than at baseline ($p < 0.001$). For the negative control, mean BI scores increased statistically significantly after two weeks of treatment ($p < 0.001$).

Tables

Mean Modified Gingival Index:

Treatment	Baseline	2 Weeks**
Negative Control	2.13	2.12
EOF Rinse	2.13	1.86*
Positive Control	2.14	1.80*

*Statistically significantly different from negative control ($p \leq 0.05$)

**Two-Week means are adjusted for baseline

Mean Plaque Index:

Treatment	Baseline	2 Weeks**
Negative Control	2.54	3.32
EOF Rinse	2.53	2.33*
Positive Control	2.61	2.38*

*Statistically significantly different from negative control ($p \leq 0.05$)

**Two-Week means are adjusted for baseline

Mean Bleeding Index:

Treatment	Baseline	2 Weeks**
Negative Control	0.15	0.19
EOF Rinse	0.16	0.11*
Positive Control	0.17	0.10*

*Statistically significantly different from negative control ($p \leq 0.05$)

**Two-Week means are adjusted for baseline

The EOF rinse was considered "at least as good as" the EO rinse, the positive control, as the upper limits of the one-sided 97.5% confidence intervals for the difference between the means for the EOF rinse and the positive control for both mean Modified Gingival Index and mean Plaque Index, 6.1% and 3.8% respectively, were below the 10% limit. The differences in means between the two treatments were 3.0% and 2.1%, relative to the positive control, for mean Modified Gingival Index and mean Plaque Index respectively.

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Safety Results: There were few adverse events in this two-week study. There were a total of seven adverse events: Herpes Simplex outbreak (1); seasonal allergy (1); flu syndrome (1); infection (2); lymphadenopathy (1); pharyngitis (1). None of these was judged to be serious or life threatening. Given the small numbers of adverse events in this study, there appeared to be no predominant adverse events and there were no treatment-related adverse events.

Conclusions: In this two week no oral hygiene model, EOF rinse was: a) efficacious in reducing gingival inflammation with concomitant antiplaque efficacy by a statistically significant greater reduction in gingival inflammation and plaque (and gingival bleeding) than the negative control, and b) "at least as good as" the positive control, the EO mouthrinse, in inhibition of gingival inflammation and plaque.