CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A6431085

Protocol Title: AN EVALUATOR-BLINDED, RANDOMIZED, PARALLEL CONTROLLED STUDY OF NICORETTE® FRESHMINT GUM VS NICORETTE® MICROTAB IN HEALTHY SMOKERS MOTIVATED TO QUIT SMOKING AND WITH VISIBLE STAINING OF TEETH

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Publications Based on the Study: None

Study Initiation and Completion Dates: 18 July 2005 to 10 November 2005

Phase of Development: Phase 4

Study Objectives:

Primary objective was to assess extrinsic stain reduction from baseline while quitting smoking using either Nicorette® Freshmint Gum (nicotine polacrilex) or Nicorette® Microtab (nicotine betacyclodextrin).

Secondary objectives were to assess: (i) Changes in intrinsic tooth shade from baseline while quitting smoking using either Nicorette® Freshmint Gum or Nicorette® Microtab; (ii) Any changes in teeth staining or teeth shade in relation to usage of gums; (iii) Gum usage patterns; (iv) Smoking status; (v) Safety.

METHODS

Study Design: This evaluator-blinded, randomized, 12-week parallel-group controlled trial compared Nicorette® Freshmint gum versus Nicorette® Microtab in healthy smokers who were motivated to quit smoking and who had visible staining of teeth.

The trial comprised five visits (baseline, Weeks 1, 2, 6, and 12). At baseline, subjects were provided with a standardized toothpaste and toothbrush; use of any other oral hygiene or tooth-whitening products was prohibited. At all visits after baseline, smoking status and use of study treatment was checked. Teeth staining and teeth shade were rated at baseline and at 2, 6 and 12 weeks using the modified Lobene Stain Index and the Vita® Shade Guide, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled were male and females aged 18-65 years, daily smokers who had been smoking for at least 1 year. Participants were motivated to quit smoking, and willing to use nicotine gum or sublingual tablet. Eligible subjects had to have normal chewing abilities (able to use chewing gum) and be willing to refrain from dental prophylaxis throughout the trial. A minimum of 20 natural teeth was required, with at least 10 of the 12 anterior teeth (numbers 6-11, and 22-27) present and scorable. The test teeth

were the eight incisors; if one of the eight incisors was not present or scorable, a cuspid could be substituted. Teeth that were grossly carious, fully crowned, or extensively restored on the facial or lingual surfaces were not included in the tooth count. A total extrinsic facial tooth stain score ≥28, according to the MacPherson Modification of the Lobene Stain Index, was required.

Subjects using other tobacco-containing products, or other NRT, or undergoing any other treatment for tobacco dependence were excluded. Subjects with orthodontic appliances, gross periodontal disease or signs of gross oral neglect, a history of oral cancer or a history of temporo-mandibular joint disorders were also excluded. Women who were pregnant, lactating or intended to become pregnant were not enrolled.

Study Treatment: The trial products were Nicorette® Freshmint gum 2 mg and 4 mg. The reference product was Nicorette® Microtab 2 mg. After being randomized to the gum or tablet, subjects were stratified according to their baseline level of nicotine dependence. High nicotine-dependent smokers received nicotine 4 mg gum, or were instructed to use a 4 mg dosage of the Microtab (2 x 2 mg tablets), while low nicotine-dependent smokers received nicotine 2 mg gum or were instructed to use a 2 mg dosage of the Microtab to help them quit. Subjects were advised to use the treatment frequently, according to the product labeling, in order to minimize or avoid symptoms of tobacco withdrawal. Study medication was used for 12 weeks.

Nicorette Freshmint 2 mg Gum	Lot number GD922A
Nicorette Freshmint 4 mg Gum	Lot number GC962A
Nicorette Microtab 2 mg	Lot number GB196G

Efficacy Evaluations: The primary efficacy parameter was the mean change in the total modified extrinsic tooth stain score, using the MacPherson modification of the Lobene Stain Index, between baseline and 6 weeks.

Secondary parameters were: mean change in modified extrinsic tooth stain score (total) between baseline and 2 and 12 weeks; mean change in modified extrinsic lingual/palatal surface stain score, modified extrinsic facial surface stain score, and modified extrinsic tooth stain score for gingival, interproximal, and body regions between baseline and 2, 6 and 12 weeks; mean change in modified extrinsic tooth stain area and intensity scores from baseline at 2, 6 and 12 weeks; change in tooth shade, measured by the Vita® Shade Guide, between baseline and 2, 6, and 12 weeks; number of pieces of nicotine gum or sublingual tablets used**;** smoking status.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Not applicable.

Safety Evaluations: Adverse events were assessed throughout the study.

Statistical Methods: Primary and secondary variables were analyzed based on data from modified intent-to-treat subjects, defined as all randomized subjects who had used study treatment and who had baseline and post-baseline assessments. Treatments were compared using ANCOVA using treatment and nicotine dependence as factors and the corresponding baseline measurement as a covariate. Each comparison was tested at the 0.05 level, two-sided. Within treatment change from baseline were made using a paired t-test.

RESULTS

Subject Disposition and Demography: 200 subjects (104 male, 96 female) were enrolled in the study. Their mean age was 35.7 years. At baseline, subjects smoked a mean of 19.2±8.0 cigarettes/day, and their mean FTND score was 4.5±2.44; 57% of subjects had made 2-5 quit attempts. At baseline, the total mean stain index was 4.2±1.53 and the mean Vita Shade score was 10.4±3.24. 102 subjects received Nicorette Gum, and 98 received Nicorette Microtab. A total of 102 subjects completed the 12-week trial.

Efficacy Results: **Primary Variable** At Week 6, the mean total stain index was statistically significantly lower in the Freshmint Gum group compared to baseline (4.01 vs 4.16, p=0.018). In the Microtab group the mean total stain index at Week 6 was higher than that at baseline. The difference between Gum vs Microtab was statistically significant (p=0.005) in favor of gum.

Statistically significant improvements in lingual stain index, body region stain index, and total stain area were also noted with Freshmint Gum versus Microtab at Week 6. Treatment with Freshmint Gum did not improve facial stain index or total stain intensity at Week 6; however, the increases in facial stain index and total stain intensity in the Freshmint Gum group at Week 6 were smaller than the corresponding increases in the Microtab group.

In the Freshmint Gum group, the mean tooth shade at Week 6 was statistically significantly lighter than at baseline (11.08 vs 10.80, p=0.023). Freshmint Gum was significantly superior to Microtab in terms of shade lightening at Week 6 (p=0.011). The change in tooth shade from baseline with Freshmint Gum represented an improvement of 0.28 on the Vita Shade Guide.

Secondary Variables Both Freshmint Gum and Microtab effectively aided smoking cessation; at Week 12, 36/102 subjects (35.3%) in the Freshmint Gum group and 37/98 subjects (37.8%) in the Microtab group had stopped smoking (biochemically validated self-reported abstinence).

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Not applicable.

Safety Results: The most common treatment-related AEs were gastrointestinal disorders (reported by 21.6% of Gum and 36.7% of Microtab users), headache (22.5% vs 17.3%), sore mouth, hiccups, and cough. Most treatment-related AEs were mild. No serious treatment-related AEs occurred during the study. One subject in the Gum group discontinued treatment because of AEs that were probably or possibly related to treatment (mild nausea and headache).

Discussion: The improvements in stain that occurred with Freshmint Gum were primarily due to reductions in staining on the lingual surfaces, but not on the facial surfaces, where one would expect most improvement due to the chewing action. The reductions in total stain were primarily due to reductions in stain area, rather than reductions in intensity. These findings suggest that Freshmint Gum had most impact on removal of newer stain, and less impact on removal of older stain.

Although the stain index reduction from baseline in the Freshmint Gum group is modest, it is worth noting that in contrast, the Microtab group showed an increase in stain from baseline. This increase in stain in the Microtab group is likely to be as a result of the dietary habits of this

traditionally heavy tea drinking population. Thus the reduction in stain in the gum group suggests an inhibitory effect on stain formation and progression in addition to the statistically significant modest stain removal found in this study. Baseline stain removal followed by subsequent measurement of stain inhibition may be worth including in future studies.

Conclusion(s): Freshmint Gum statistically significantly reduced the mean total stain score at Week 6 versus baseline. In the between-treatment comparison, Freshmint Gum was significantly superior to Microtab in terms of stain reduction at Week 6.

Compared to Microtab, Freshmint Gum statistically significantly improved lingual stain index, total stain area, and tooth shade at Week 6.

Freshmint Gum statistically significantly improved the mean tooth shade at Week 6 versus baseline. In the between-treatment comparison, Freshmint Gum was significantly superior to Microtab in terms of tooth lightening at Week 6.

The results of this study confirm that chewing Nicorette Freshmint Gum as recommended in a 'real world' active smoking cessation program produces a statistically significant change in the parameter of whitening as measured via influence on reversing stain versus baseline, as well as versus the negative control (Microtab) at the primary time point (Week 6). The Vita Shade Guide (the secondary index) supported the trend of stain improvement. These results support the efficacy of Nicorette Freshmint Gum in arresting the progression of tooth stain.