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| <b>Study No.:</b> Z7871335                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Title:</b> A Pilot Clinical Study Investigating the Efficacy of a Toothpaste in Providing Immediate and Short Term Relief from Dental Hypersensitivity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale:</b> Clinical studies have demonstrated immediate relief from dentine hypersensitivity (DH) following direct application of a toothpaste to the dentine (by massaging the sensitive tooth with toothpaste), termed a 'dab-on' application. Recently, an alternative method of treatment application, where each sensitive tooth was brushed with toothpaste prior to brushing the whole mouth, has been shown to provide relief from DH within minutes for a stannous fluoride containing toothpaste. The aim of the study was to replicate this alternative methodology by determining the ability of a stannous fluoride containing toothpaste to provide immediate and short term relief (up to 14 days) from DH compared to a control toothpaste.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Phase:</b> III                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Study Period:</b> 6 September 2011 to 28 September 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Study Design:</b> A randomized, examiner blind, negative controlled, two treatment arm, parallel group, and single-site study. Subjects included in the study had at least two sensitive teeth that met the eligibility criteria at the screening and baseline visit.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Centres:</b> Single centre in USA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Indication:</b> Dental Hypersensitivity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Treatment:</b> Subjects were randomized to two treatment groups. Subjects assigned with the test treatment (a commercially available toothpaste from United States containing 0.454% stannous fluoride) brushed the 2 selected sensitive teeth with a study toothbrush for 30 seconds each first and then the whole mouth thoroughly for at least 1 minute, while those assigned the negative control (toothpaste containing 1100 ppm sodium fluoride) brushed their whole mouth thoroughly with a study toothbrush for at least 1 minute after which sensitivity was assessed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Objectives:</b> The primary objective was to compare the efficacy of a test toothpaste against that of a control toothpaste in reducing dental hypersensitivity, immediately following use, as measured by Schiff Sensitivity Score.<br><br>The secondary objectives included comparison of the efficacy of a test toothpaste against that of a control toothpaste in reducing dental hypersensitivity, immediately following use, as measured by tactile threshold (Yeaple probe) and, following twice daily brushing for 3 and 14 days, as measured by Schiff Sensitivity Score and tactile threshold (Yeaple probe). The exploratory objective included evaluation of reduction in dental hypersensitivity of a test toothpaste against that of a control toothpaste immediately and after twice daily brushing for 3 and 14 days, as measured by a Visual Analogue Scale (VAS), and determination of level of subject familiarity with their allocated study product, post treatment, as measured by subject responses to a 'product familiarity' questionnaire                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Primary Efficacy:</b> Difference in evaporative (air) sensitivity (Schiff Sensitivity Score) between the test and control group immediately following the treatments.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Secondary Efficacy:</b> Difference between the test and control group, in evaporative (air) sensitivity (Schiff Sensitivity Score) as assessed on Day 3 and Day 14 and tactile sensitivity threshold (Yeaple Probe) immediately after application and as assessed on Day 3 and Day 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Other Efficacy:</b> Difference in VAS scores between the test and control group immediately following the treatments, and as assessed on Day 3 and Day 14. Exploratory analyses were carried out on Product Familiarity questions asked at Day 14 to gauge subject familiarity with their assigned study toothpaste.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Statistical Methods:</b> .The primary analysis population for the assessment of efficacy was the intent to treat (ITT) population.<br><br>The primary efficacy variable was the mean treatment difference between groups at the immediate time point. The change in Schiff Sensitivity Score was analyzed immediately following treatment using Analysis of Covariance (ANCOVA) with fixed effect factors for treatment group and baseline Schiff Sensitivity Score as a covariate. The change in tactile threshold was analyzed immediately following treatment using ANOVA with fixed effect factor for treatment group. The Schiff Sensitivity Score assessment and tactile sensitivity (Yeaple probe) analysis were repeated at Day 3 and Day 14 as secondary analyses. Exploratory analyses were carried out on VAS. VAS was analyzed at the immediate time point, Day 3 and Day 14 using ANCOVA with fixed effect factors for treatment group and baseline VAS as a covariate. From the above models, 95% confidence intervals (CIs) and p-value were also provided. In addition, to assess efficacy within treatments, the mean change from baseline within each treatment group and the adjusted mean change from baseline (with 2-sided 95% CIs) were also presented from the above models. P-values testing whether within treatment change from baseline is zero were also provided. All significance tests were conducted at the two-sided 5% significance level. Exploratory analyses carried out on product |

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| familiarity questions were descriptive and determined in terms of frequency and percentages.                                                                                                                                                                                                                                                                                                                                                                                                 |                |
| <b>Study Population:</b> Healthy adult, male and female subjects, aged 18-65 years, in good general health and suffering from tooth sensitivity [measured by tactile stimulus (Yeaple probe, tactile threshold 10g) and evaporative (air) stimulus (Schiff Sensitivity Score $\geq 2$ )] were included. Subjects were excluded if there was any known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients. |                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Overall</b> |
| Number of Subjects:                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                |
| Planned, N                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 120            |
| Randomised, N                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 118            |
| Completed, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 117 (99.2)     |
| Total Number Subjects Withdrawn, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1 (0.8)        |
| Withdrawn due to Adverse Events, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0              |
| Withdrawn due to Lack of Efficacy, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0              |
| Withdrawn for other reasons, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1 (0.8)        |
| <b>Demographics</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>Overall</b> |
| N (ITT population)                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 118            |
| Females: Males                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 74:44          |
| Mean Age, years (SD)                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 36.3 (10.30)   |
| American Indian or Alaska native, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 18 (15.3)      |
| Asian, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 9 (7.6)        |
| Black or African American, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 32 (27.1)      |
| Native Hawaiian or other Pacific Islander, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                             | 7 (5.9)        |
| White, N (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 52 (44.1)      |

| <b>Primary Efficacy Variables:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |            |                                            |                                            |                         |                     |       |         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------------------------------------------|--------------------------------------------|-------------------------|---------------------|-------|---------|
| Sensitivity Parameter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Time point | 0.454% stannous fluoride toothpaste        | 1100 ppm sodium fluoride toothpaste        | Difference <sup>b</sup> | 95% CI <sup>*</sup> |       | P value |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |            | Adjusted change from baseline <sup>a</sup> | Adjusted change from baseline <sup>a</sup> |                         |                     |       |         |
| Schiff <sup>c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Immediate  | -0.42                                      | -0.32                                      | -0.10                   | -0.26               | 0.06  | 0.2294  |
| * From ANCOVA model with factors: treatment, baseline Schiff as covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |            |                                            |                                            |                         |                     |       |         |
| <sup>a</sup> Baseline only included those subjects who have a corresponding post-baseline assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                            |                                            |                         |                     |       |         |
| <sup>b</sup> Differences in adjusted mean change from baseline represent 0.454% stannous fluoride toothpaste minus 1100 ppm sodium fluoride toothpaste Protection                                                                                                                                                                                                                                                                                                                                                                                                                       |            |                                            |                                            |                         |                     |       |         |
| <b>Secondary Efficacy Variables:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                            |                                            |                         |                     |       |         |
| Sensitivity Parameter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Time point | 0.454% stannous fluoride toothpaste        | 1100 ppm sodium fluoride toothpaste        | Difference <sup>b</sup> | 95% CI <sup>*</sup> |       | P value |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |            | Adjusted change from baseline <sup>a</sup> | Adjusted change from baseline <sup>a</sup> |                         |                     |       |         |
| Schiff                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Day 3      | -0.57                                      | -0.45                                      | -0.12                   | -0.30               | 0.06  | 0.1792  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Day 14     | -1.24                                      | -0.72                                      | -0.52                   | -0.74               | -0.30 | <0.0001 |
| Tactile                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Immediate  | 3.73                                       | 3.81                                       | -0.08                   | -2.49               | 2.32  | 0.9445  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Day 3      | 4.83                                       | 6.90                                       | -2.07                   | -5.38               | 1.25  | 0.2200  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Day 14     | 15.85                                      | 7.16                                       | 8.69                    | 3.96                | 13.43 | 0.0004  |
| * From ANCOVA model with factors: treatment, baseline Tactile threshold as covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                            |                                            |                         |                     |       |         |
| <sup>a</sup> Baseline only included those subjects who have a corresponding post-baseline assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                            |                                            |                         |                     |       |         |
| <sup>b</sup> Difference in adjusted mean change from baseline represent 0.454% stannous fluoride toothpaste minus 1100 ppm sodium fluoride toothpaste such that a negative difference favours stannous fluoride toothpaste                                                                                                                                                                                                                                                                                                                                                              |            |                                            |                                            |                         |                     |       |         |
| <b>Other Efficacy Variables:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |            |                                            |                                            |                         |                     |       |         |
| Sensitivity Parameter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Time point | 0.454% stannous fluoride toothpaste        | 1100 ppm sodium fluoride toothpaste        | Difference <sup>b</sup> | 95% CI <sup>*</sup> |       | P value |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |            | Adjusted change from baseline <sup>a</sup> | Adjusted change from baseline <sup>a</sup> |                         |                     |       |         |
| VAS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Immediate  | -11.29                                     | -7.97                                      | -3.32                   | -7.85               | 1.22  | 0.1500  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Day 3      | -17.16                                     | -13.48                                     | -3.68                   | -9.43               | 2.06  | 0.2070  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Day 14     | -30.30                                     | -23.28                                     | -7.02                   | -13.72              | -0.33 | 0.0400  |
| * From ANCOVA model with factors: treatment and baseline VAS as covariate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |            |                                            |                                            |                         |                     |       |         |
| <sup>a</sup> Baseline only included those subjects who have a corresponding post-baseline assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                            |                                            |                         |                     |       |         |
| <sup>b</sup> Difference in adjusted mean change from baseline represent 0.454% stannous fluoride toothpaste minus 1100 ppm sodium fluoride toothpaste such that a negative difference favours stannous fluoride toothpaste                                                                                                                                                                                                                                                                                                                                                              |            |                                            |                                            |                         |                     |       |         |
| For responses to product familiarity questions, post completion of the 14 day brushing period, in answer to the question "Do you think you have been using an active sensitivity toothpaste", 42 (71.2%) and 29 (49.15%) subjects in the 0.454% stannous fluoride and 1100 ppm sodium fluoride groups answered the question correctly. For question 2 "Can you identify the product you think you were using from this list", response to question 2 was "CORRECT" for 4 (6.78%) subjects in 0.454% stannous fluoride group and 42 (71.19%) subjects in 1100 ppm sodium fluoride group. |            |                                            |                                            |                         |                     |       |         |

**Safety Results:** All subjects who were randomized and received at least one dose of study treatment were considered evaluable for the safety population. An on therapy adverse event (AE) was defined as an AE with onset on or after the start of study treatment but not later than 5 days after the last administration of study treatment.

| Adverse Events              | 0.454% stannous fluoride toothpaste | 1100 ppm sodium fluoride toothpaste |
|-----------------------------|-------------------------------------|-------------------------------------|
| Subjects with any AE, N (%) | 0                                   | 0                                   |

**Serious Adverse Events**

No SAE occurred on either treatment

**Conclusion:**

This study did not replicate the conclusions regarding a better immediate and ongoing sensitivity relief for a stannous fluoride dentifrice in comparison to a sodium monofluorophosphate dentifrice as published in clinical results by He, et.al., 2011 for the Stannous Fluoride toothpaste; specifically.

Statistically significant differences between Stannous Fluoride toothpaste and Control (sodium fluoride toothpaste) were not observed for Schiff and Tactile scores until Day 14 of twice daily brushing with a novel brushing technique.

No significant differences between treatments were observed at the immediate and Day 3 time points for Schiff, Tactile and VAS scores. The subjects in 1100ppm sodium fluoride group were better at correctly identifying which product they were using when in fact answering 'No' constituted a correct answer as these subjects weren't using a sensitivity toothpaste. Both products were well-tolerated in this study.

Reference:

He T, Barker M, Qaqish J, Sharma N. Fast Onset Sensitivity Relief of a 0.454% Stannous Fluoride Dentifrice. J Clin Dent 2011; 22:46-50.

**Publications:**