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Personalized Care and Oral Health Innovation: Delivering Evidence Across a Spectrum Of Patient Needs

Every patient that presents to our dental practice is unique. One patient is in the middle of orthodontic treatment, another has a history of periodontal disease with complicating diabetes. A new patient presents with difficulty controlling malodor. A patient you have treated since childhood is now a grown, pregnant woman with inflamed gingivae. A middle-aged man has generally good oral health, but an increasing number of deepening pocket-depths at each recall visit.

As each patient presents with individual needs, the home care instructions you give for between-visit hygiene are equally unique. What may be appropriate for one patient to achieve and maintain his/her oral health goals is inadequate for the treatment goals of another patient.

This 2019 Special Issue of *The Journal of Clinical Dentistry* contains five articles that provide clinical trial evidence for a number of patient-specific conditions. Since the launch of the first Sonicare electric toothbrush over twenty-five years ago, the Philips Oral Healthcare portfolio has grown and diversified. With each new innovation, however, we maintain the same commitment to ensuring the safety and performance of each new product.

The gold-standard for meeting this expectation is to run well-designed, well-controlled clinical trials. The articles contained here give you a transparent look at the outcomes of these clinical studies. In brief, we include an article that reports on a regimen designed to improve oral malodor, with another article that provides details on a regimen designed for patients during orthodontic treatment. And, as daily plaque control continues to be the cornerstone of achieving long-term oral health, we report on the safety and efficacy of a number of different Sonicare brush heads, as well as brushing modes, to reduce supragingival plaque and gingival inflammation.

While my full-time role for the last eight years has been to lead the Clinical and Dental Scientific Affairs team at Philips Oral Healthcare, I still maintain a clinical practice. Like you, *in vivo* evidence helps me to make better decisions for my patients. The articles contained in this Special Issue act as a bridge between these two ends. They provide you and me a rigorous look into the safety and efficacy performance of innovative products and regimens. Do these innovations improve outcomes better than standard-of-care? Are they safe for daily use? Are they effective alternatives to other available options for a given patient condition? The clinical studies presented here were designed with these very questions in mind.

At Philips, we are committed to making a meaningful difference across a spectrum of patient-care needs. As a dentist, I am committed to ensuring that my patients have effective home care tools and instructions. The evidence presented here provides you the opportunity to see how the innovation platform of Philips Oral Healthcare can help your patients achieve their personal oral health treatment goals.

Marilyn Ward, DDS

Director, Clinical and Dental Scientific Affairs
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Contents

The Effects of Use of a Powered and a Manual Home Oral Hygiene Regimen on Plaque and Gum Health in an Orthodontic Population

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Abstract

- **Objective:** The objective of this study was to compare the effect of two home use oral hygiene regimens on plaque, gingivitis, and gingival bleeding on subjects undergoing orthodontic treatment with fixed appliances.
- **Methods:** This was a randomized, parallel, single-center clinical trial. Eligible study subjects fit the following profile: age 12–65 years; non-smoker; plaque score of ≥ 2.0 per Bonded Bracket Index (BBI) on dentition with fixed orthodontic hardware; minimum of 10 orthodontic brackets in each arch or on all teeth from first molar to first molar; presenting with mild to moderate gingivitis, defined as a score of ≥ 1 on at least 20 sites per Gingival Bleeding Index (GBI). Subjects with advanced periodontal disease or gingival recession were not eligible. Eligible subjects were randomized to one of two home use oral hygiene regimens: manual toothbrush plus string floss (used with a threading device) for interdental cleaning (MTF regimen); or Philips Sonicare EasyClean power toothbrush with InterCare brush head and AirFloss Pro powered device, used with BreathRx mouthrinse for interdental cleaning (Sonicare Orthodontic Regimen or SOR). All subjects brushed twice daily with standard fluoridated dentifrice and performed interdental cleaning once daily. Efficacy and safety examinations were performed at Baseline and following three and six weeks of home use of the study products, and included assessments of BBI, GBI, Modified Gingival Index (MGI), and Modified Plaque Index (MPI).
- **Results:** Of 228 enrolled subjects, 223 were included in the primary analysis. For the primary endpoint, reduction in BBI score following three weeks of product use, the overall least squares (LS) mean (95% CI) reduction was 0.89 (0.84, 0.95) for SOR and 0.06 (0.01, 0.12) for MTF. Expressed as percent reduction (95% CI) from Baseline, this was 33.1% (31.1%, 35.2%) for SOR and 2.01% (-0.06%, 4.07%) for MTF. The differences between regimens were statistically significant, $p < 0.0001$. Statistically significant differences between regimens were observed in BBI following six weeks of product use, and also for all other efficacy variables (GBI, MGI, MPI) at Week 3 and Week 6.
- **Conclusion:** The powered oral hygiene regimen was significantly more effective than a manual regimen in reducing plaque on bracketed and non-bracketed teeth, and in reducing gingival bleeding and gingival inflammation in orthodontic subjects following three weeks of use and persisting following six weeks of use. All products were safe on oral tissues and fixed orthodontic appliances.

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Introduction

Treatment with fixed orthodontic appliances is not without risk to the oral health of the patient. There are clinically observable adverse responses in the surrounding hard and soft oral tissues that are commonly associated with treatment. As the presence of brackets and arch wires can hinder a patient's ability to comprehensively clean tooth surfaces, along the gingival margin and in interproximal spaces, residual food and debris are more readily retained and removed with more difficulty in this population. Protracted retention of debris can alter the quantity and character of the surrounding plaque biofilm,[1,2] increasing the periodontopathogens and the pH-based cariogenicity in the oral environment.[3]

Local changes in the biofilm, consistent with a lower pH, favor the proliferation of acidogenic and aciduric bacterial species such as *Streptococcus mutans* and *Lactobacilli.* The proliferation of these organisms and their by-products can hamper remineralization mechanisms [4,5] which creates an enamel environment that is susceptible to the development of white spot lesions (WSL) or caries.[6]

Periodontal health can also be affected by the presence of fixed orthodontic appliances, with gingival inflammation, gingival bleeding, or pocket depths observed to negatively increase during treatment.[7-11]

Gingival enlargement, resulting from inflamed gingival tissue, further complicates the patient's ability to comprehensively remove plaque from tooth surfaces.[4] This sets the stage for a physiologic and ecological feedback loop that favors disease-promoting factors. And while these effects may be transient in some patients, returning to a more baseline character once brackets are removed,[12] there can be significant detriments such as chronically enlarged soft tissues, WSL or caries, all of which may require invasive intervention after debonding. It is incumbent on the dental practitioner to educate the patient on adequate oral hygiene practices at the onset of, and during, orthodontic treatment, thus to limit these potential risks of treatment.

The ultimate goal is patient motivation and compliance, with optimal oral hygiene practices throughout often lengthy treatment. A particular challenge is that orthodontic patients, predominantly

adolescents, are a population group who may not be inclined toward preventive health habits. The oral hygiene habits a patient brings to treatment are difficult to change, especially so because orthodontic appliances makes each oral hygiene encounter more laborious.

Interdental cleaning with string floss, for example, requires the use of specialized floss or a threading device, which requires both additional time and dexterity of the user. Tooth brushing is similarly affected. Brushing previously smooth tooth surfaces, now obstructed by bulky brackets and wires, requires additional attention and care in order to adequately remove debris and plaque.

The current clinical study was conducted to explore whether the adoption of a hygiene regimen consisting of powered devices confers clinical benefits compared to a standard of care manual hygiene approach, so as to elicit whether adoption of the powered regimen could potentially help mitigate the commonly observed risks in an orthodontic population.

It has been previously reported that the use of a power toothbrush is superior to a manual toothbrush in reducing plaque and gingivitis.[13-16] As a category, the devices are designed with features that encourage compliance, there are brush head models specifically optimized to target patient-specific conditions, and the devices have powerful motors that drive brush head movement to a much greater extent than could reasonably be achieved manually.

Similarly, novel powered devices have been designed to aid the user in performing interdental cleaning. Powered interdental cleaners, such as the Philips Sonicare AirFloss, were designed to overcome the challenges of usability associated with string floss, while retaining the same level of efficacy.[17]

The regimens tested in this six-week study were comprised of either a manual toothbrush plus string floss (MTF), or a Philips Sonicare EasyClean powered toothbrush with InterCare brush head, and a powered interdental cleaning device, Sonicare AirFloss Pro, used with an antimicrobial rinse, BreathRx, in the fluid reservoir (Philips, Bothell, WA, USA). The clinical endpoints included the assessment of surface plaque on bracketed and non-bracketed surfaces, as well as clinical assessment of gingival inflammation and gingival bleeding.

Materials and Methods

Study Design and Objectives

This was a randomized, parallel clinical trial. This study was reviewed and approved by an accredited Institutional Review Board (US IRB; Miami, FL, USA). All subjects screened and enrolled in the study provided informed consent and/or assent, as applicable. The ethical principles regarding the treatment of human subjects on study were consistent with the tenets outlined in the Declaration of Helsinki.

There were a total of three study visits over a period of six weeks. Table I provides a depiction of study visits and procedures. The primary objective of the study was to compare the effect of the Sonicare Orthodontic Regmien (SOR) to a standard control regimen, manual toothbrush plus floss (MTF), to reduce plaque on bracketed teeth, per the Bonded Bracket Index[18] (BBI) following three weeks of home product use.

The secondary objectives of the study were to assess the safety of the products on oral tissues, and to compare the effects of SOR and MTF on the reduction of plaque on bracketed teeth, per BBI, following six weeks of product home use, and after three and six weeks of product use on the following: reduction of gingival inflammation per Modified Gingival Index[19] (MGI); the reduction of gingival bleeding per Gingival Bleeding Index[20] (GBI); and the reduction of plaque on non-bracketed dentition per Lobene and Soparker Modified Plaque Index[21-23] (MPI).

Table I
Study Visits and Procedures

Visit Number	Time Point	Description of Procedures
1	Day 0	Informed Consent/Assent Medical/Dental History Oral Exam MGI, GBI, BBI, MPI Randomization to SOR or MTF Product Dispense and Instruction Provide Diary for Compliance Tracking
3-6 hours Plaque Accumulation		
2	Week 3	Compliance Monitoring Adverse Events Monitoring MGI, GBI, BBI, MPI Provide Diary for Compliance Tracking
3-6 hours Plaque Accumulation		
3	Week 6	Compliance Monitoring Adverse Events Monitoring MGI, GBI, BBI, MPI Dismiss from Study

Efficacy and Safety Measurements

The BBI was performed to assess plaque on the surface of teeth with orthodontic fixtures. Plaque scores were recorded on four sites per tooth, on a scale of 0 to 3. For teeth without brackets, the MPI was used to assess plaque on 6 sites per tooth, on a scale of 0 to 5.

Gingival inflammation was assessed according to the MGI, full mouth, on four sites per tooth, on a scale of 0 to 4. Gingival bleeding was evaluated using the GBI on four sites per tooth, on a scale of 0 to 3. Table II provides a description and scale utilized for each index.

Safety was assessed by examiner interview at study visits, by intraoral tissue exam, and by subject report on a home diary card used throughout the study.

The examiners who performed clinical assessments scored a given index for all study subjects, for all visits, thus to eliminate variability as a result of inter-examiner scoring differences.

Study Subjects

Eligible study subjects met the following study entry criteria: age 12–65 years; non-smoker, presenting with at least 10 orthodontic brackets on teeth in each arch, or brackets on all teeth from first molar to first molar; have a minimum average plaque score of ≥ 2.0 based on the BBI following 3–6 hours plaque accumulation; and have a GBI of ≥ 1 on at least 20 sites. Subjects were not eligible if any of the following were present: a diagnosis of insulin dependent diabetes; xerostomia; current use of antibiotics; prescription-dose anti-inflammatory medications or anticoagulants, excessive gingival recession or heavy deposits of calculus; or were pregnant or nursing.

Treatment Groups

There were two treatment groups evaluated in this clinical trial. Subjects were assigned to home use of either the Sonicare Orthodontic

Table II
Description of Scoring Methodology; BBI, MPI, MGI, GBI

0	1	2	3	4	5
Bonded Bracket Index (BBI) Partial Mouth; Teeth with Brackets					
No plaque or debris	plaque covering less than 1/3 of the tooth area, separate flecks of plaque on the tooth	plaque covering 1/3 to 2/3 of the tooth area, moderate accumulation of plaque	plaque covering more than 2/3 of the tooth area, high accumulation of plaque	**N/A**	**N/A**
Lobene and Soparkar Modification of Quigley and Hein Plaque Index (MPI) Partial Mouth; 3 Sites per Surface; 6 Sites per Tooth Performed on Teeth without Brackets					
No plaque	separate flecks of plaque at the gingival margin	a thin continuous band of plaque (up to 1mm) at the cervical margin of the tooth	a band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth	plaque covering at least 1/3 but less than 2/3 of the crown of the tooth	covering 2/3 or more of the crown of the tooth
Modified Gingival Index (MGI) Full Mouth; 4 Sites per Tooth Except for Last Site in Each Arch					
Absence of inflammation	mild inflammation; slight change in color little change in texture of any portion of but not the entire margin or papillary gingival unit	mild inflammation but involving entire margin or papillary unit	moderate inflammation; glazing, redness, edema and/or hypertrophy of margin or papillary unit	severe inflammation; marked redness, edema and/or hypertrophy of marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration	**N/A**
Gingival Bleeding Index Full Mouth; 4 Sites per Tooth Except for Last Site in Each Arch					
No bleeding	bleeding on gently probing	bleeding appears immediately upon gently probing	spontaneous bleeding which is present prior to probing	**N/A**	**N/A**

Regimen (SOR), consisting of a Philips Sonicare EasyClean power toothbrush with an InterCare Brush Head, followed by interproximal cleaning with Philips Sonicare AirFloss Pro (Figure 1) utilized with BreathRx mouthrinse (active ingredient: cetylpyridinium chloride 0.075%) in the fluid reservoir, or a standard control regimen (MTF) consisting of an ADA reference manual toothbrush and interproximal cleaning with Reach® Unflavored Waxed Floss (Johnson & Johnson, New Brunswick, NJ, USA), which was utilized with a threading device. Subjects in both treatment groups brushed twice daily using fluoride-containing Crest® Cool Mint Gel dentifrice (Procter & Gamble, Cincinnati, OH, USA) and performed interproximal cleaning once daily. The use of any other hygiene product or device was prohibited during the study period.

Randomization, Controls to Minimize Bias, and Data Capture

Eligible subjects were randomized to one of two treatment groups, SOR or MTF. Randomization was balanced for gender and age, for approximately equal distribution between treatment groups. The age strata were defined as 12–18 years and 19–65 years. The study examiners who performed the efficacy measurements (BBI, MPI, MGI, GBI) were blinded to the treatment assignment of subjects. Study data were collected on a web-based electronic data capture (EDC) system. Access to the system was limited by log-in credentials of database users based on assigned study role.

Statistical Methods

Sample Size Determination. The primary objective of this study was to compare plaque reduction on bracketed teeth (per BBI) for SOR and MTF following three weeks of use. Based on previous studies comparing a Sonicare power toothbrush and a manual toothbrush on non-bracketed teeth, the observed difference for MPI ranged from 0.14 to 0.85, with a standard deviation (SD) range from 0.19 to 0.43.

Figure 1. *Mechanical devices, sonicare ortho regimen. Pictured left: Philips Sonicare EasyClean electric toothbrush with InterCare brush head. Pictured right: Philips Sonicare AirFloss Pro.*

Expressed as a percent reduction in MPI, observed differences ranged from 6.4% to 31%, with a standard deviation range from 7.04 to 15.06. Overall, a minimum difference in plaque reduction between a power toothbrush and a manual toothbrush of 0.2 (SD = 0.44) and 10% (SD = 15%) was established to be of clinical relevance.

For this study, due to the addition of adjunct interproximal cleaning (either AirFloss Pro with rinse or string floss), a difference between the regimens of SOR and MTF of approximately 80% of the acceptable difference, as defined above for power and manual toothbrushes (*i.e.*, 0.16 for plaque reduction, 8% for percent reduction), was considered to be clinically relevant. Furthermore, it was assumed that the scoring methodologies of BBI and MPI would produce similar outcomes.

Based on these general assumptions, a sample size of 112 subjects per treatment group would allow for greater than 80% power to detect a difference in BBI between SOR and MTF.

General Considerations. All analyses were performed on the modified intent to treat (mITT) population, which included all randomized subjects with a complete plaque evaluation post three weeks of product home use. Subjects were analyzed according to the randomized treatment assignment. The analysis of safety included all randomized subjects. All analyses were conducted using SAS® software (SAS, Cary, NC, USA).

Demographics. Demographics (*e.g.*, age, gender) were summarized for all mITT subjects by treatment group and overall. For continuous characteristics, number of non-missing observations, mean, SD, 95% confidence interval (CI) of the mean, median, minimum (Min), and maximum (Max) were presented. One way analysis of variance (ANOVA) was used to compare the means between treatment groups. For categorical characteristics, the frequency count and the percentage of subjects in each category were presented. The Chi-Square test or Fisher's exact test, as appropriate, was used to compare the incidence of the categorical variable between treatment groups.

Primary Efficacy Analysis. The primary efficacy measure for this study was plaque reduction on bracketed teeth following three weeks of home use of the assigned study products. Plaque score on bracketed teeth was evaluated using the BBI index. Three summary BBI scores were calculated from the whole mouth for each subject as efficacy endpoints, which included: the average score at each visit, calculated as the sum of scores of all evaluable sites divided by the number of evaluable sites; the reduction from Baseline score at each follow-up visit, calculated as Baseline average score minus post-Baseline average score; and percent reduction from Baseline score at each follow-up visit, calculated as the score reduction from Baseline divided by the Baseline average score x 100.

Boxplots are presented to show the distributions of the average BBI score at each study visit for both treatment groups. The lower and upper boundary of the box marks the 25th and 75th, respectively, percentile of observed values; the line intersecting the box indicates the median; the circle within the box indicates the mean; and the lower and upper whisker denotes the Min and Max, respectively, of the observed values. The least square mean (LSM), the standard error (SE), and the two-sided 95% CI of the mean for the three summary BBI scores were estimated for each treatment group at each visit using ANOVA models, adjusting for the Baseline BBI as a covariate. The two-sided 95% CI for the mean difference between the treatment groups was also constructed.

Secondary Efficacy and Safety Analysis. The secondary efficacy measures were the reduction in gingivitis assessed by MGI, the reduction in gingival bleeding assessed by GBI, the reduction in plaque on non-bracketed teeth assessed by MPI after three and six weeks of home use, and plaque reduction on bracketed teeth assessed by BBI after six weeks of home use. Analysis was performed for each study visit for the three summary scores derived from each corresponding index using a similar approach as described above for the primary analysis.

Safety outcomes were provided in listings of adverse events, as well as for abnormal findings indicated on oral exam.

Results

Demographics

There were 228 subjects who provided informed consent (including assent, where appropriate) and were screened for the study. All of these subjects were enrolled and randomized. Of these, 223 subjects were included in the mITT analysis at Week 3, with 113 subjects in the SOR group, and 110 in the MTF group (two subjects were lost to follow-up, two subjects decided to terminate early, and one subject missed the Week 3 visit). Summary of demographics for the mITT study population is presented in Table III. The mean age of subjects was 16.0 years with 144 female subjects (64.6%) and 79 male subjects (35.4%). There were no statistical differences in the age and gender distribution of subjects between groups.

Primary Efficacy Results

Bonded Bracket Index (Bracketed Teeth). A boxplot indicating the distribution of average BBI scores at Baseline, Week 3, and Week 6 is presented in Figure 2. The mean Baseline scores were comparable for both treatment groups.

Table IV provides a complete depiction of the primary efficacy results for BBI. The LS mean (95% CI) reduction in BBI following three weeks of product use was 0.89 (0.84, 0.95) for SOR and 0.06 (0.01, 0.12) for MTF. This difference was statistically significant, $p < 0.0001$. Expressed as percent BBI reduction from Baseline, the outcomes were 33.1% (31.1%, 35.2%) for SOR and 2.01% (-.0.06%, 4.07%) for MTF.

At the Week 6 time point, the LS Mean (95% CI) reduction in BBI was 1.02 (0.98, 1.06) for SOR and 0.11 (0.06, 0.15) for MTF. This difference was statistically significant, $p < 0.0001$. Expressed as percent BBI reduction from Baseline, the Week 6 outcomes were 37.9% (36.2%, 39.5%) for SOR and 3.74% (2.06%, 5.42%) for MTF.

Table III
Subjects Demographics, mITT Population

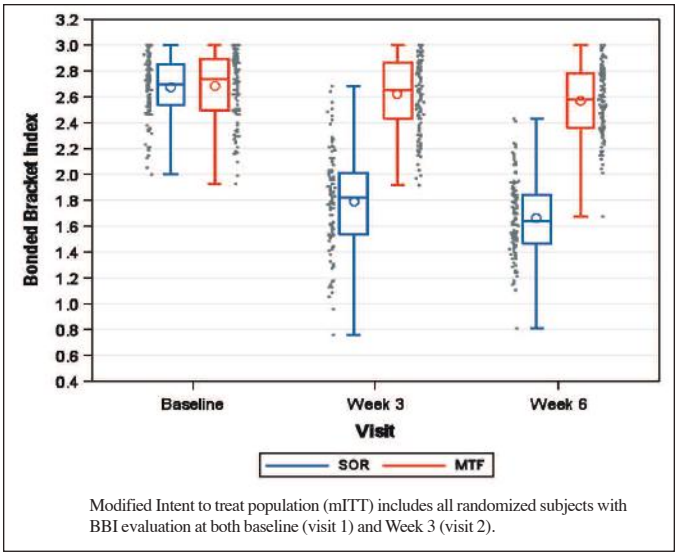
		Treatment			
Parameter	Category	SOR (N=115, rand)	MTF (N=113, rand)	Total (N=228)	p-value[a]
Age (yrs.)	No. Subjects	113	110	223	0.5233
	Mean(SD)	16.3 (8.9)	15.6 (7.1)	16.0 (8.1)	
	95% CI	(14.7, 18.0)	(14.3, 17.0)	(14.9, 17.0)	
	Median	14	13	13	
	Min, Max	(12, 63)	(12, 47)	(12, 63)	
Gender	Female	73 (64.6%)	71 (64.5%)	144 (64.6%)	0.9930
	Male	40 (35.4%)	39 (35.5%)	79 (35.4%)	

[a]p-value is based on one-way analysis of variance for continuous variables, and Chi-squared test for categorical variables.

Secondary Efficacy Results

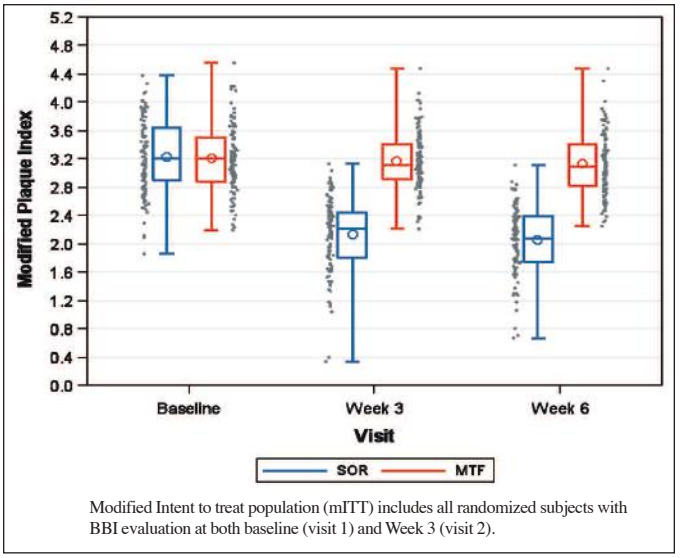
Modified Plaque Index (Non-Bracketed Teeth). A boxplot indicating the distribution of average MPI scores at Baseline, Week 3, and Week 6 is presented in Figure 3. Both treatment groups had a similar distribution at Baseline.

Table IV provides a complete depiction of MPI analyses. For MPI, the differences observed between products at both the Week 3 and Week 6 time points were statistically significant, $p < 0.0001$. At Week 3, the LS mean (95% CI) reduction in MPI was 1.09 (1.01, 1.18) for SOR and 0.05 (-0.04, 0.13) for MTF. Expressed as percent MPI reduction from Baseline, the outcomes were 32.7% (30.2%, 35.1%) for SOR and 0.26% (-2.25%, 2.76%) for MTF.



Modified Intent to treat population (mITT) includes all randomized subjects with BBI evaluation at both baseline (visit 1) and Week 3 (visit 2).

Figure 2. *Distribution of outcomes, BBI, Baseline, Week 3, Week 6.*



Modified Intent to treat population (mITT) includes all randomized subjects with BBI evaluation at both baseline (visit 1) and Week 3 (visit 2).

Figure 3. *Distribution of outcomes, MPI, Baseline, Week 3, Week 6.*

Table IV
Summary Analysis, Bonded Bracket Index, and Modified Plaque Index

		Treatment			
Variable	Statistic	SOR (N=113)[c]	MTF (N=110)	Difference[a]	p-value[b]
Bonded Bracket Index					
Baseline	LS Mean (SE)	2.68 (0.02)	2.68 (0.02)	-0.00 (0.03)	0.9889
	95% CI	(2.63, 2.73)	(2.63, 2.73)	(-0.07, 0.07)	
Reduction from Baseline					
Week 3	LS Mean (SE)	0.89 (0.03)	0.06 (0.03)	0.83 (0.04)	<0.0001
	95% CI	(0.84, 0.95)	(0.01, 0.12)	(0.75, 0.91)	
Week 6	LS Mean (SE)	1.02 (0.02)	0.11 (0.02)	0.91 (0.03)	<0.0001
	95% CI	(0.98, 1.06)	(0.06, 0.15)	(0.85, 0.98)	
%Reduction from Baseline					
Week 3	LS Mean (SE)	33.12 (1.04)	2.01 (1.05)	31.11 (1.47)	<0.0001
	95% CI	(31.08, 35.16)	(-0.06, 4.07)	(28.20, 34.02)	
Week 6	LS Mean (SE)	37.88 (0.85)	3.74 (0.85)	34.13 (1.20)	<0.0001
	95% CI	(36.21, 39.54)	(2.06, 5.42)	(31.77, 36.50)	
Modified Plaque Index					
Baseline	LS Mean (SE)	3.23 (0.05)	3.20 (0.05)	0.04 (0.07)	0.5947
	95% CI	(3.14, 3.32)	(3.11, 3.29)	(-0.09, 0.16)	
Reduction from Baseline					
Week 3	LS Mean (SE)	1.09 (0.04)	0.05 (0.04)	1.05 (0.06)	<0.0001
	95% CI	(1.01, 1.18)	(-0.04, 0.13)	(0.94, 1.16)	
Week 6	LS Mean (SE)	1.17 (0.04)	0.09 (0.04)	1.09 (0.06)	<0.0001
	95% CI	(1.09, 1.25)	(0.01, 0.17)	(0.97, 1.20)	
%Reduction from Baseline					
Week 3	LS Mean (SE)	32.65 (1.25)	0.26 (1.27)	32.39 (1.79)	<0.0001
	95% CI	(30.18, 35.12)	(-2.25, 2.76)	(28.87, 35.91)	
Week 6	LS Mean (SE)	35.11 (1.26)	1.52 (1.27)	33.59 (1.78)	<0.0001
	95% CI	(32.64, 37.58)	(-0.98, 4.01)	(30.08, 37.11)	

Modified Intent to treat population (mITT) includes all randomized subjects with BBI evaluation at both baseline (visit 1) and Week 3 (visit 2).
Note: Reduction and percent reduction refers to change from pre to post-treatment.
ANOVA Model for Baseline (Pre-brushing): Result=Treatment + error.
ANOVA Model for Post-baseline: Outcome = Baseline Result + Treatment + error.
[a]Diff = Mean (SE) of the treatment difference (PTB+AirFlossPro+BreathRx minus MTB+StringFloss).
[b]p-value is based on a fixed effects ANOVA model F-test (Ho: All treatments are equal).
[c]There were 112 subjects analyzed at Week 6, SOR treatment group

At Week 6, the LS Mean (95% CI) reduction in MPI was 1.17 (1.09, 1.25) for SOR and 0.09 (0.01, 0.17) for MTF. Expressed as percent reduction from Baseline, the outcomes were 35.1% (32.6%, 37.6%) for SOR and 1.52% (-0.98%, 4.01%) for MTF.

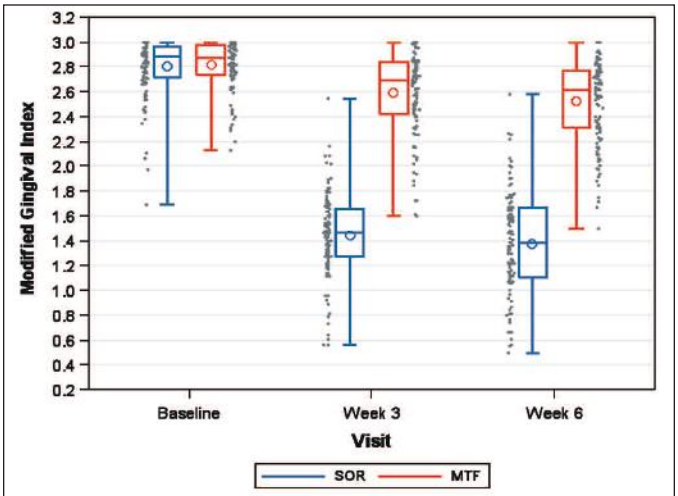
Modified Gingival Index. A boxplot indicating the distribution of average MGI scores at Baseline, Week 3, and Week 6 is presented in Figure 4. The mean Baseline values were balanced for both treatment groups.

Table V provides a complete depiction of MGI analyses. The differences observed in MGI between products at both the Week 3 and Week 6 time points were statistically significant, $p < 0.0001$. At Week 3, the LS Mean (95% CI) reduction in MGI was 1.36 (1.30, 1.41) for SOR and 0.23 (0.17, 0.28) for MTF. Expressed as percent reduction from Baseline, these outcomes were 48.5% (46.6%, 50.5%) for SOR and 8.15% (6.14%, 10.2%) for MTF.

At Week 6, the LS Mean (95% CI) reduction in MGI was 1.43 (1.36, 1.49) for SOR and 0.30 (0.23, 0.36) for MTF. Expressed as percent reduction from Baseline, the outcomes were 51% (48.7%, 53.3%) for SOR and 10.5% (8.21%, 12.9%) for MTF.

Gingival Bleeding Index. A boxplot indicating the distribution of average GBI scores at Baseline, Week 3 and Week 6 is presented in Figure 5. The mean Baseline values were balanced for both treatment groups.

Table V provides a complete depiction of GBI analyses. For GBI, the differences observed between products at both the Week 3 and Week 6 time points were statistically significant, $p < 0.0001$. At Week 3, the LS Mean (95% CI) reduction in GBI was 0.33 (0.31, 0.35) for SOR and 0.07 (0.05, 0.09) for MTF. Expressed as percent reduction



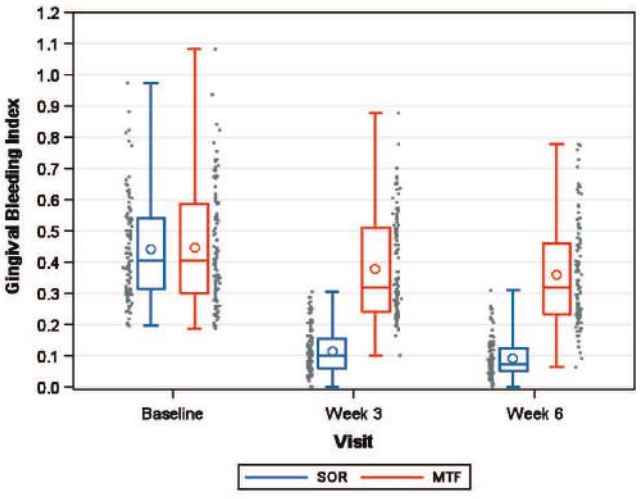
Modified Intent to treat population (mITT) includes all randomized subjects with BBI evaluation at both baseline (visit 1) and Week 3 (visit 2).

Figure 4. *Distribution of outcomes, MGI, Baseline, Week 3, Week 6.*

Table V
Summary Analysis, Modified Gingival Index, and Gingival Bleeding Index

		Treatment			
Variable	Statistic	SOR (N=113)[c]	MTF (N=110)	Difference[a]	p-value[b]
Modified Gingival Index					
Baseline	LS Mean (SE)	2.80 (0.02)	2.82 (0.02)	-0.02 (0.03)	0.5621
	95% CI	(2.76, 2.84)	(2.78, 2.86)	(-0.07, 0.04)	
Reduction from Baseline					
Week 3	LS Mean (SE)	1.36 (0.03)	0.23 (0.03)	1.13 (0.04)	<0.0001
	95% CI	(1.30, 1.41)	(0.17, 0.28)	(1.05, 1.21)	
Week 6	LS Mean (SE)	1.43 (0.03)	0.30 (0.03)	1.13 (0.05)	<0.0001
	95% CI	(1.36, 1.49)	(0.23, 0.36)	(1.04, 1.22)	
%Reduction from Baseline					
Week 3	LS Mean (SE)	48.54 (1.01)	8.15 (1.02)	40.40 (1.43)	<0.0001
	95% CI	(46.56, 50.53)	(6.14, 10.15)	(37.57, 43.22)	
Week 6	LS Mean (SE)	50.99 (1.17)	10.54 (1.18)	40.46 (1.66)	<0.0001
	95% CI	(48.69, 53.30)	(8.21, 12.86)	(37.18, 43.73)	
Gingival Bleeding Index					
Baseline	LS Mean (SE)	0.44 (0.02)	0.44 (0.02)	-0.00 (0.02)	0.9351
	95% CI	(0.41, 0.47)	(0.41, 0.48)	(-0.05, 0.04)	
Reduction from Baseline					
Week 3	LS Mean (SE)	0.33 (0.01)	0.07 (0.01)	0.26 (0.01)	<0.0001
	95% CI	(0.31, 0.35)	(0.05, 0.09)	(0.24, 0.29)	
Week 6	LS Mean (SE)	0.35 (0.01)	0.09 (0.01)	0.27 (0.01)	<0.0001
	95% CI	(0.33, 0.37)	(0.07, 0.10)	(0.24, 0.29)	
%Reduction from Baseline					
Week 3	LS Mean (SE)	73.59 (2.25)	10.96 (2.28)	62.64 (3.20)	<0.0001
	95% CI	(69.17, 78.02)	(6.47, 15.44)	(56.33, 68.94)	
Week 6	LS Mean (SE)	78.33 (2.12)	16.15 (2.14)	62.18 (3.02)	<0.0001
	95% CI	(74.14, 82.51)	(11.93, 20.38)	(56.23, 68.12)	

Modified Intent to treat population (mITT) includes all randomized subjects with BBI evaluation at both baseline (visit 1) and Week 3 (visit 2).
Note: Reduction and percent reduction refers to change from pre to post-treatment.
ANOVA Model for Baseline (Pre-brushing): Result=Treatment + error.
ANOVA Model for Post-baseline: Outcome = Baseline Result + Treatment + error.
[a]Diff = Mean (SE) of the treatment difference (PTB+AirFlossPro+BreathRx minus MTB+StringFloss).
[b]p-value is based on a fixed effects ANOVA model F-test (Ho: All treatments are equal).
[c]There were 112 subjects analyzed at Week 6, SOR treatment group



Modified Intent to treat population (mITT) includes all randomized subjects with BBI evaluation at both baseline (visit 1) and Week 3 (visit 2).

Figure 5. *Distribution of outcomes, GBI, Baseline, Week 3, Week 6.*

from Baseline, the outcomes were 73.6% (69.2%, 78.0%) for SOR and 11.0% (6.47%, 15.4%) for MTF.

At Week 6, the Overall LS Mean (95% CI) reduction in GBI was 0.35 (0.33, 0.37) for SOR and 0.09 (0.07, 0.10) for MTF. Expressed as percent reduction from Baseline, the outcomes were 78.3% (74.1%, 82.5%) for SOR and 16.2% (11.9%, 20.4%) for MTF.

Safety

There were no adverse events reported in the study.

Discussion and Conclusions

Within the limits and controls of this study, the outcomes indicate that the use of the powered regimen for home oral hygiene was statistically significantly superior to standard-of-care manual toothbrush plus floss regimen, in all clinical measures, at all time points, in a population of subjects with fixed orthodontic hardware. This includes the reduction of surface plaque on both bracketed and non-bracketed teeth, the reduction of inflamed gingival tissue, and the reduction in gingival bleeding.

The outcomes observed here are important for several reasons. First, it provides the practitioner with evidence from a randomized, controlled clinical trial setting that implementation of the regimen tested here has been demonstrated to be both safe and significantly more effective than the standard of care approach. This may be particularly important in an adolescent population, where compliance to the practitioner-prescribed home care regime can be a significant challenge over the course of orthodontic treatment.

Second, the more pronounced surface plaque removal observed in the powered regimen group may disrupt the feedback loop that elevates the risk of associated sequelae commonly observed during treatment as effects to periodontal health, and the development of white spot or carious lesions. That is to say, where fixed hardware harbor food and debris, promoting biofilm proliferation of a more disease-associated character, reducing the burden of surface plaque through powered brushing and interdental cleaning may help to minimize these effects. As these changes to the oral environment have been clinically established as risk factors,[24] and which pervasively persist in spite of myriad management efforts,[25] hygiene solutions aimed at minimizing plaque proliferation and an ensuing transition to microbiological dysbiosis, may stand to have a salient and sustainable impact on a patient's oral health over the course of orthodontic treatment. The growing body of evidence that associates an inflammatory oral environment with other inflammation-associated human diseases[26-28] underscores the importance of practitioner-driven education, and greater patient-centric care, aimed at the minimizing changes to a patient's gingival status during orthodontic treatment.

It is acknowledged that this study was limited in scope to only those metrics that can be clinically observed and quantified within a reasonably finite time period. Additional studies to measure the effects upstream of clinical expression would be interesting to evaluate, thus to adequately understand the mechanisms that are affected following introduction of plaque control via the powered regimen. Are the clinical changes in surface plaque, gingivitis, and bleeding reflective of a change of character of the microbial milieu and the environmental pH, for example? Further, does optimized plaque control help minimize the incidence and severity of white spot and/or carious lesions over the course of orthodontic treatment? As also concluded in a systematic review regarding fluoride use and enamel demineralization during orthodontic treatment,[29] longer-term, controlled studies, including these endpoints, would be needed to answer these important questions.

The partnership between the practitioner and the patient is to help ensure that the aesthetic and functional benefits of orthodontic treatment are not at the cost of a patient's oral health. The results of the powered home hygiene regimen tested here provide evidence that there are measurable advantages that are both quickly evident (within three weeks) and sustained (at Week 6) in plaque biofilm removal and gingivitis reduction, over a standard of care approach. These outcomes may facilitate clinical decisions that are aimed at improving oral health management over the course of a patient's orthodontic treatment.

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Conflict of Interest: K. Nammi, E. M. Starke, S-S Ou, M. Ward, and W. Jenkins are employed by Philips Oral Healthcare. J. Milleman and K. Milleman are employed by Salus Research.

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A Comparison of the Effect of Two Power Toothbrushes on the Reduction of Gingival Inflammation and Supragingival Plaque

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Abstract

- **Objectives:** To compare the effect of the Philips Sonicare DiamondClean Smart and Oral-B Genius 8000 powered toothbrushes on gingivitis, gingival bleeding, and supragingival plaque reduction following 42 days of home use.
- **Methods:** This was a randomized, parallel, examiner-blinded, prospective clinical trial with two treatment groups. Eligible participants were generally healthy volunteers who were manual toothbrush users, non-flossers, 18–65 years of age. The subject panel included non-smokers with ≥ 50 sites of gingival bleeding according to the Gingival Bleeding Index (GBI), and a supragingival plaque score of ≥ 1.8 per Modified Plaque Index (MPI) at 3–6 hours following last tooth brushing encounter. Eligible subjects were randomized to use either a Philips Sonicare DiamondClean Smart with Premium Plaque Control brush head (DCS) or an Oral-B Genius 8000 with FlossAction brush head (OBG) for home use. Each toothbrush was used twice daily for two minutes. All subjects used a standardized fluoride-containing dentifrice. All other oral hygiene measures were prohibited. Subjects returned at Day 14 for an interim compliance and safety assessment, and at Day 42 for the final safety and efficacy assessments.
- **Results:** Of 222 enrolled and eligible subjects, 219 completed (112 in the SDC group, 107 in the OBG group) the study. The least squares (LS) mean and 95% confidence interval (CI) estimates for gingivitis reduction and percent reduction per Modified Gingival Index (MGI) following 42 days of product home use were 1.38 (1.30, 1.46) and 51.32% (48.45%, 54.19%) for DCS, and 0.53 (0.45, 0.61) and 20.07% (17.14%, 23.00%) for OBG. The differences, expressed as either reduction or percent reduction, were statistically significant between the two groups, $p < 0.001$. Statistically significant differences were also observed between products at Day 42 for the gingival bleeding and supragingival plaque reduction endpoints, $p < 0.001$. There were two reported adverse events.
- **Conclusions:** The Philips Sonicare DiamondClean Smart powered toothbrush reduced gingival inflammation, gingival bleeding, and supragingival plaque significantly more than the Oral-B Genius 8000 powered toothbrush following a 42-day home-use period. Both products were safe for use.

(J Clin Dent 2019;30(Spec Iss A)A9–15)

Introduction

Periodontal disease has been shown to be significantly and independently associated with other non-communicable chronic diseases.[1] These include, for example, diabetes,[2-4] rheumatoid arthritis,[5] kidney disease,[6-8] and atherosclerotic cardiovascular disease.[9-12]

The overall impact of non-communicable diseases (NCDs) on health outcomes is significant. In June 2018, the World Health Organization reported on the effects of NCDs on the global population, attributing 41 million deaths each year to these diseases; of which 15 million are premature, occurring between the ages of 30 and 69 years.[13]

That periodontal disease is an associated condition with other NCDs, and is also observed to exert inflammatory stress on tissues, as do other NCDs, preventing and treating periodontal disease is an important part of total patient care.

Fundamental to prevention and treatment is the promotion and maintenance of a health-associated biofilm,[14,15] where the oral microbial ecology is in equilibrium with the inflammatory systems of the host. The speciation and character of the biofilm has been observed to shift in its transition from health to disease.[16,17] This can initiate an inflammatory response, with the clinical expression of inflammation exhibited as edema, discoloration, and bleeding of oral gingivae. If left untreated, local inflammation can lead to the destruction of the periodontal tissues and osseous structures of teeth. For many of the above-cited NCDs, the common implicating factor between periodontal and other non-communicable disease states is characterized by inflammation, with changes in pro-inflammatory pathways observed to occur.[18-20]

It is with this understanding that the task of daily plaque management becomes more significant than simply "cleaning teeth." Working with patients to improve and maintain optimal oral hygiene is an imperative of clinical practice, particularly for patients presenting with risk factors for periodontal disease.[21] There are many available tools, medicaments, and techniques intended to aid in this regard. Transitioning patients from manual to powered tooth brushing, for example, can be a frequently recommended option. Powered toothbrushes have features that promote compliance and ease of use. Additionally, these products have motors that initiate brush head motion which far exceed what can be achieved manually.

That said, the landscape of powered tooth brushing options is vast, and to put all available technologies in the same category may not result in the desired benefit for patients when a transition from manual to powered tooth brushing is made. The current clinical trial was conducted to evaluate two marketed powered toothbrushes in order to directly compare their effects on gingivitis and plaque in a population of habitual manual toothbrush users who exhibit at least moderate levels of gingivitis.

Materials and Methods

Study Design and Objectives

This was a prospective, examiner-blinded, randomized, single-center, two-arm, parallel study with three study visits. It was reviewed and approved by the IntegReview Institutional Review Board. The study was designed to compare the safety and effectiveness of the Philips Sonicare DiamondClean Smart (DCS) with Premium Plaque Control brush head (Philips Oral Healthcare, Bothell, WA, USA) and the Oral-B Genius 8000 (OBG) with FlossAction brush head (Procter & Gamble Co., Cincinnati, OH, USA). Both power toothbrushes were used for 2 minutes, twice daily, in their respective "Clean" modes in a "non-connected" state, meaning that none of the App features were active. All subjects used Crest Cool Mint Gel dentifrice (Procter & Gamble Company, Cincinnati, OH, USA).

The objectives of the study included comparisons of safety, and effects on reducing gingivitis (inflammation and bleeding) and supragingival plaque following 42 days of home use of the assigned product. The primary endpoint was designated as the comparison of effects on gingival inflammation at Day 42. In addition, an analysis comparing the proportion of subjects with reduced gingival inflammation, reduced gingival bleeding, and reduced plaque, with predefined cut-off reduction values, was planned. Figure 1 provides a study visit schematic.

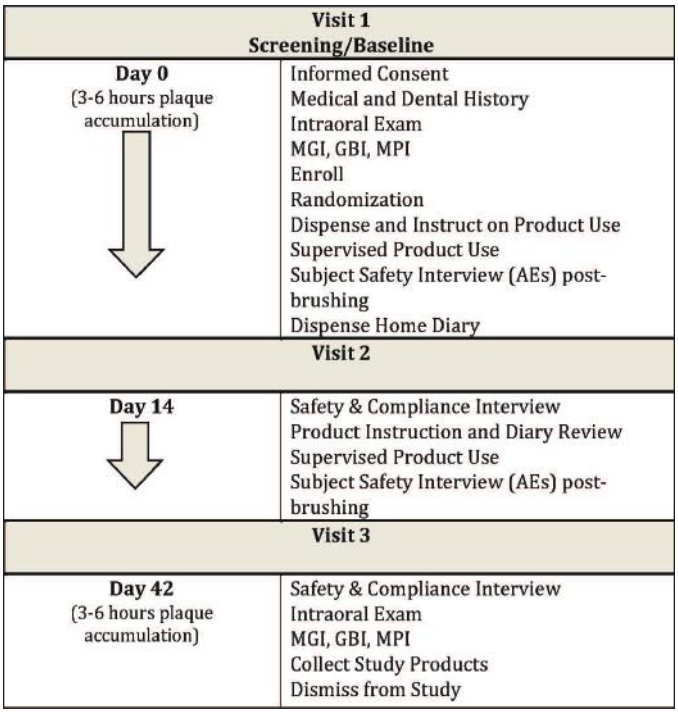

Figure 1. *Study visits and procedures.*

Efficacy and Safety Measurements

Efficacy was evaluated by two examiners trained and calibrated in the visual assessment of plaque and gingivitis per published visual clinical metrics. In this study, the following measurement methods were used: Lobene and Soparker Modified Plaque Index (MPI),[22,23] the Modified Gingival Index[24] (MGI), and the Gingival Bleeding Index (GBI).[25] Table I provides the scale and scoring classifications of each index.

Safety was assessed by oral tissue examination and by subject report on a home diary record.

Study Subjects

Eligible subjects were generally healthy manual toothbrush users between the ages of 18 and 65 years, non-smokers, non-flossers, who were able to provide informed consent and follow the planned study

Table I

Scoring Methodology for Efficacy Metrics: Plaque, Gingival Inflammation and Gingival Bleeding

Lobene and Soparker Modified Plaque Index, Six Sites[a] per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**4**	**5**
No plaque	Separate flecks of plaque at the cervical margin of the tooth	A thin continuous band of plaque (up to 1mm) at the cervical margin of the tooth	A band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth	Plaque covering at least 1/3 but less than 2/3 of the crown of the tooth	Plaque covering 2/3 or more of the crown of the tooth
Modified Gingival Index, Lobene, Six Sites[a] per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**4**	**N/A**
Absence of inflammation	Mild inflammation, slight change in color, little change in texture of the marginal or papillary gingival unit	Mild inflammation; slight change in color, little change in texture of the marginal or papillary gingival unit	Moderate inflammation; glazing, redness, edema and/or hypertrophy of margin or papillary unit	Severe inflammation; marked redness, edema and/or hypertrophy or marginal or papillary gingival unit, spontaneous bleeding, congestion or ulceration	
Gingival Bleeding Index, van der Weijden, Six Sites[a] per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**N/A**	**N/A**
No bleeding	Bleeding on gently probing	Bleeding appears immediately upon gently probing	Spontaneous bleeding which is present prior to probing		

a: Sites include: distobuccal, buccal, mesiobuccal, distolingual, lingual, mesiolingual

procedures. The study population included subjects exhibiting moderate gingivitis, defined as ≥ 50 sites of bleeding per GBI, and a plaque score of ≥ 1.8 per MPI, assessed at 3–6 hours following the subject's last oral hygiene procedure. Subjects with any of the following were excluded from participation: rampant oral decay, significant gingival recession, evidence of periodontitis or heavy deposits of calculus, pregnancy, xerostomia, insulin-dependent diabetes, the presence of orthodontic hardware or current use of prescription-dose anti-coagulant or anti-inflammatory medications. Any dental student or dental professional, clinical research site employee or their relatives were also not eligible to participate.

In the event that a subject required dental or medical care in a context that could affect a safety or efficacy endpoint of the study, or which put the subject at greater risk, the participant was removed from study at the discretion of the study investigator.

Randomization and Controls to Minimize Bias

All subjects provided informed consent prior to assessment of eligibility. Those who met the eligibility criteria were randomized to receive either a DCS or an OBG powered toothbrush for home use. Randomization was balanced for gender, such that approximately equal numbers of males and females were represented in each treatment group. Study personnel who performed randomization or product dispense and instruction, did not perform any activities related to study endpoints.

The examiners performing all study efficacy evaluations (MGI, GBI, MPI) were blinded to the assigned powered toothbrush allocation for each subject. Scoring proficiency and accuracy of each examiner (intra-calibration) was previously established. The examiner of a given index performed scoring of that index for all subjects, at all visits, eliminating potential bias due to inter-examiner scoring differences.

For study subjects, the use of any other oral hygiene device or medicament was prohibited during the study period.

Data Capture

Study data were captured on a secure, web-based data system with programmed logic and edit-checks that are compliant to the standards of 21 CFR Part 11. To appropriately maintain the integrity of the data, access to the system was limited by log-in credentials that matched the study role of the user (*e.g.*, blinded or un-blinded). Study data were monitored by sponsor staff or designee to ensure accuracy of recording and reporting.

Statistical Methods

Sample Size Determination. A prior study[26] was conducted in which power toothbrushes from each of these product platforms (Sonicare and Oral-B) were compared. The study included a comparable study population, as well as similar endpoint and timepoint assessments. The outcomes of that study, at Day 42, showed that the Sonicare powered toothbrush was superior to the Oral-B powered toothbrush, with a difference in MGI reduction of 0.48 and an MGI percent reduction difference of 19%, as well as a difference in MPI reduction of 0.50 and an MPI percent reduction difference of 17%.

In the current study, a clinically significant difference in MGI reduction greater than 0.2, with a common standard deviation (SD) of 0.45 and a percent reduction of 8% with a common SD of 18%, was deemed sufficient to differentiate DCS and OBG. Using these assumptions, a minimum sample size of 108 subjects in each group would allow for approximately 90% power to detect a difference between the two products, using a two-sided t-test with a 0.05 significance level.

With regard to the secondary endpoints (GBI and MPI), this sample size would also allow for more than 85% power (0.05 significance level) to detect a difference in GBI reduction of 0.10 (common SD = 0.3) or 13% (common SD = 30%), and more than 90% power (0.05 significance level) to detect a difference in MPI reduction of 0.2 (common SD = 0.45) or 8% (common SD = 18%).

General Considerations. The primary efficacy analysis was performed including all randomized subjects with Baseline and Day 42 gingivitis evaluations (modified intent to treat, mITT). Subjects were analyzed according to the randomized treatment assignment. The analysis of safety included all randomized subjects.

All variables were summarized by descriptive statistics. Continuous variables were summarized using the number of non-missing observations, mean, median, standard deviation (SD), minimum, and maximum. Categorical variables were summarized using the frequency count and the percentage of subjects in each category. All analyses were conducted using SAS® software (SAS, Cary, NC, USA).

Efficacy Endpoints. The efficacy indices, MGI, GBI, and MPI, at each tooth site were scored using the scoring methodology described in Table I. A standardized data collection form was used to capture these data at each study visit. The efficacy endpoints were the reduction from baseline, calculated as the Baseline score minus the post-Baseline score; and percent reduction from Baseline, calculated as the reduction in score divided by the Baseline score times 100. For each subject, these two endpoints were summarized for the whole mouth (Overall) and by region of the mouth (*i.e.*, anterior, posterior, interproximal, and posterior interproximal). For each index, analyses were performed separately for each endpoint and for each region.

Primary Efficacy Analysis. The primary efficacy measure for this study was the reduction in gingivitis score from Baseline to Day 42. The efficacy analysis included all randomized subjects with an MGI score at Baseline and Day 42. Comparisons between the two treatment groups for reduction and percent reduction from Baseline were performed using an ANOVA model with the Baseline score as a covariate.

Least square (LS) mean, standard error (SE) of the mean, and two-sided 95% confidence intervals (CI) were presented by treatment group. Comparisons between treatment groups were performed using an F-test.

Secondary Efficacy Analysis. The secondary efficacy measures of the study were the reduction in gingival bleeding (GBI) and plaque (MPI) from Baseline to Day 42. The analysis evaluating these endpoints used a similar method as described above for the primary endpoint.

In addition, a proportion analysis was completed for each efficacy endpoint at Day 42 at prescribed cut-off values. The 95% confidence intervals of the proportion analyses were also presented. Furthermore, comparisons of the separate proportions between the two treatment groups were performed using a Chi-square or Fisher's exact test, as

appropriate. The cut-off values of observed reduction of MGI, GBI, or MPI were as follows:

Reduction from Baseline to Day 42 ≥ 0.1
Reduction from Baseline to Day 42 ≥ 0.2
Reduction from Baseline to Day 42 ≥ 0.3
Percent reduction from Baseline to Day 42 ≥ 10%
Percent reduction from Baseline to Day 42 ≥ 15%
Percent reduction from Baseline to Day 42 ≥ 20%

Safety Analysis

Adverse events and oral examination abnormalities were presented in data listings.

Results

Demographics

Two-hundred twenty-eight subjects provided informed consent and were screened for the study. Of these, 222 were enrolled and randomized, with 219 subjects completing the study. Of the three subjects who did not complete the study, two were lost to follow-up and one withdrew from the study. Table II provides a depiction of subject enrollment and completion.

Table II
Subject Enrollment and Completion

Subjects Screened N= 228					
Screen Failures N=6	Enrolled N=222				
	Not Randomized N=0	Randomized N=222			
		DCS N=113		OBG N=109	
		C[a] N=112	D[b] N=1	C N=107	D N=2

a: completed
b: discontinued

The mean (SD) age of subjects was 40.3 (12.4) years. There were 175 (79.9%) female participants, and 44 (20.1%) male participants who completed the study. No significant differences were observed in the distribution of age and gender between the two treatment groups.

Primary Efficacy Results

Modified Gingival Index. The distribution, mean, median, and 25th-75th percentile of observed values for MGI are presented in a boxplot in Figure 2. The analyses for MGI outcomes at Baseline and Day 42, including reduction and percent reduction, as well as the proportion analysis, are presented in Table III.

For the primary efficacy endpoint, reduction in MGI at Day 42, the Overall LS mean reduction, and percent reduction (95% CI) was 1.38 (1.30, 1.46) and 51.32% (48.45%, 54.19%) for DCS, and 0.53 (0.45, 0.61) and 20.07% (17.14%, 23.00%) for OBG. Both reduction and percent reduction comparisons were statistically significant, $p < 0.001$.

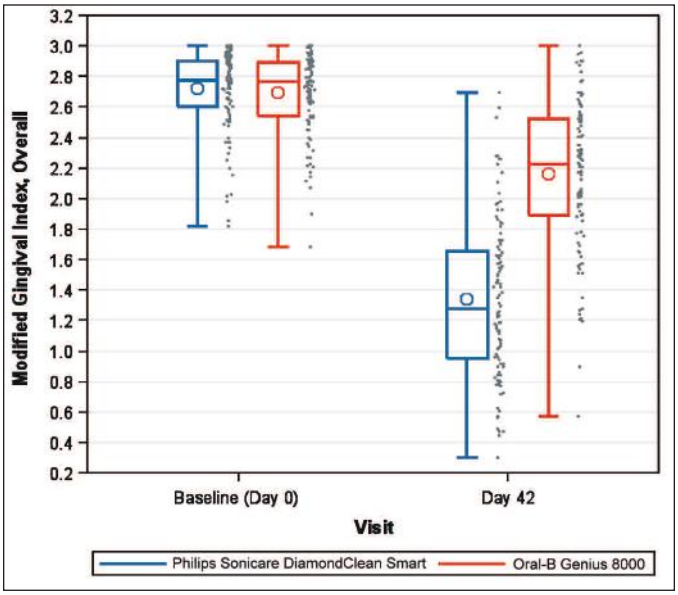

Figure 2. *Boxplot of Modified Gingival Index, overall, by treatment group at Baseline and Day 42. Note: Each dot represents a single observation.*

Table III
Modified Gingival Index, Reduction, Percent Reduction and Proportion Analysis, Overall, at Baseline, and Day 42

Variable	Statistic	DCS (N=112)	OBG (N=107)	Difference	p-value
Baseline (Day 0)	LS Mean (SE) 95% CI	2.72 (0.02) (2.67, 2.77)	2.69 (0.03) (2.64, 2.74)	0.02 (0.04) (-0.05, 0.09)	0.5172
Day 42	LS Mean (SE) 95% CI	1.33 (0.04) (1.25, 1.40)	2.18 (0.04) (2.10, 2.25)	-0.85 (0.06) (-0.96, -0.74)	<0.0001
Reduction from Baseline					
Day 42	LS Mean (SE) 95% CI	1.38 (0.04) (1.30, 1.46)	0.53 (0.04) (0.45, 0.61)	0.85 (0.06) (0.74, 0.96)	<0.0001
Percent Reduction from Baseline					
Day 42	LS Mean (SE) 95% CI	51.32 (1.46) (48.45, 54.19)	20.07 (1.49) (17.14, 23.00)	31.25 (2.08) (27.14, 35.35)	<0.0001
Proportion Analysis: Reduction from Baseline at Day 42					
RFB[a] > = 0.3	n (Prop.) 95% CI	111 (99.1%) (95.1%, 100.0%)	78 (72.9%) (63.4%, 81.0%)		<0.001
Proportion Analysis: Percent Reduction from Baseline at Day 42					
PRFB[b] > = 20%	n (Prop.) 95% CI	106 (94.6%) (88.7%, 98.0%)	50 (46.7%) (37.0%, 56.6%)		<0.001

a: Reduction from Baseline
b: Percent reduction from Baseline

For brevity, only the highest cut-off value (expressed as percent of subjects and 95% CI) in the proportion analysis is presented here, with 99.1% (95.1%, 100.0%) DCS subjects improving by a margin of at least 0.3. For OBG, the corresponding value was 72.9% (63.4%, 81.0%) subjects. The difference between outcomes was statistically significant, $p < 0.001$.

Secondary Efficacy Results

Gingival Bleeding Index. The distribution of observed GBI outcomes is presented in a boxplot in Figure 3. The analysis for GBI outcomes at Baseline and Day 42, including reduction and percent reduction, as well as the proportion analysis, are presented in Table IV.

For GBI, the overall LS mean reduction and percent reduction (95% CI) at Day 42 were 0.42 (0.39, 0.44) and 72.78% (68.95%, 76.60%) for DCS, and 0.29 (0.26, 0.31) and 48.86% (44.95%, 52.78%) for OBG. Both reduction and percent reduction comparisons were statistically significant, $p < 0.001$.

For the proportion analysis, 74.1% (65.0%, 81.9%) DCS subjects improved GBI score by a margin of at least 0.3. The corresponding proportion for OBG subjects was 38.3% (29.1%, 48.2%). The difference between outcomes was statistically significant, $p < 0.001$.

Modified Plaque Index. The distribution of observed MPI outcomes is presented in a boxplot in Figure 4. The analysis for MPI outcomes at Baseline and Day 42, including reduction and percent reduction, as well as the proportion analysis, are presented in Table V.

For MPI, the overall LS mean reduction and percent reduction (95% CI) at Day 42 were 0.67 (0.61, 0.73) and 22.20% (20.08%, 24.31%) for DCS, and 0.32 (0.25, 0.38) and 10.56% (8.40%, 12.73%) for OBG. Both reduction and percent reduction comparisons were statistically significant, $p < 0.001$.

For the proportion analysis, 85.7% (77.8%, 91.6%) of DCS subjects improved MPI score by a margin of at least 0.3. The corresponding value for OBG subjects was 51.4% (41.5%, 61.2%). The difference between outcomes was statistically significant, $p < 0.001$.

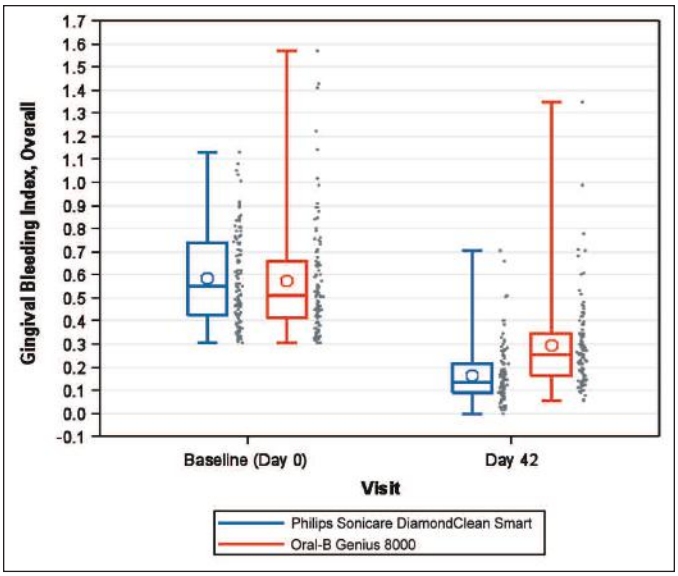

Figure 3. *Boxplot of Gingival Bleeding Index, overall, by treatment group at Baseline and Day 42. Note: Each dot represents a single observation.*

Safety

There were two adverse events reported. The first, gingival abrasion, was mild and assessed as possibly related to the study product. The second event, patient reported bleeding gums, was moderate and assessed as related to the study product. Both events occurred in the OBG treatment group and both were resolved upon conclusion of the study.

Discussion and Conclusions

Within the limits and controls of this study, the comparison of the two devices on the common hallmarks of oral health indicate that use of the Philips Sonicare DiamondClean Smart powered toothbrush was superior to use of the Oral-B Genius 8000 powered toothbrush in its ability to reduce gingival inflammation, gingival bleeding, and surface plaque after a home use period of 42 days. In addition, with only two adverse events (one mild and one moderate) reported

Table IV

Gingival Bleeding Index, Reduction, Percent Reduction and Proportion Analysis, Overall, at Baseline and Day 42

Variable	Statistic	DCS (N=112)	OBG (N=107)	Difference	p-value
Baseline (Day 0)	LS Mean (SE) 95% CI	0.59 (0.02) (0.54, 0.63)	0.58 (0.02) (0.53, 0.62)	0.01 (0.03) (-0.05, 0.07)	0.7319
Day 42	LS Mean (SE) 95% CI	0.16 (0.01) (0.14, 0.19)	0.30 (0.01) (0.27, 0.32)	-0.13 (0.02) (-0.17, -0.10)	<0.0001
		Reduction from Baseline			
Day 42	LS Mean (SE) 95% CI	0.42 (0.01) (0.39, 0.44)	0.29 (0.01) (0.26, 0.31)	0.13 (0.02) (0.10, 0.17)	<0.0001
		Percent Reduction from Baseline			
Day 42	LS Mean (SE) 95% CI	72.78 (1.94) (68.95, 76.60)	48.86 (1.99) (44.95, 52.78)	23.91 (2.78) (18.44, 29.38)	<0.0001
		Proportion analysis: Reduction from Baseline at Day 42			
RFB[a] > = 0.3	n (Prop.) 95% CI	83 (74.1%) (65.0%, 81.9%)	41 (38.3%) (29.1%, 48.2%)		<0.0001
		Proportion analysis: Percent Reduction from Baseline at Day 42			
PRFB[b] > = 20%	n (Prop.) 95% CI	111 (99.1%) (95.1%, 100.0%)	97 (90.7%) (83.5%, 95.4%)		0.0042

a: Reduction from Baseline
b: Percent reduction from Baseline

Table V
Modified Plaque Index, Percent Reduction and Proportion Analysis, Overall, at Baseline, Day 14, Day 42

Variable	Statistic	DCS (N=112)	OBG (N=107)	Difference	p-value
Baseline (Day 0)	LS Mean (SE) 95% CI	3.00 (0.04) (2.92, 3.07)	3.00 (0.04) (2.92, 3.07)	0.00 (0.05) (-0.11, 0.11)	0.9965
Day 42	LS Mean (SE) 95% CI	2.33 (0.03) (2.26, 2.39)	2.68 (0.03) (2.62, 2.74)	-0.35 (0.05) (-0.44, -0.26)	<0.0001
		Reduction from Baseline			
Day 42	LS Mean (SE) 95% CI	0.67 (0.03) (0.61, 0.73)	0.32 (0.03) (0.25, 0.38)	0.35 (0.05) (0.26, 0.44)	<0.0001
		Percent Reduction from Baseline			
Day 42	LS Mean (SE) 95% CI	22.20 (1.07) (20.08, 24.31)	10.56 (1.10) (8.40, 12.73)	11.63 (1.54) (8.61, 14.66)	<0.0001
		Proportion analysis: Reduction from Baseline at Day 42			
RFB[a] > = 0.3	n (Prop.) 95% CI	96 (85.7%) (77.8%, 91.6%)	55 (51.4%) (41.5%, 61.2%)		<0.0001
		Proportion analysis: Percent Reduction from Baseline at Day 42			
PRFB[b] > = 20%	n (Prop.) 95% CI	62 (55.4%) (45.7%, 64.8%)	16 (15.0%) (8.8%, 23.1%)		<0.0001

a: Reduction from Baseline
b: Percent reduction from Baseline

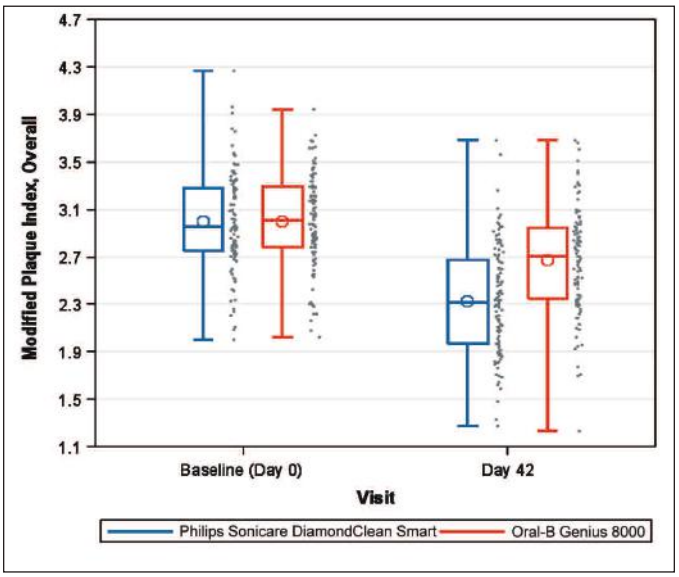

Figure 4. *Boxplot of Modified Plaque Index, Overall, by Treatment Group at Baseline and Day 42. Note: Each dot represents a single observation.*

from a population of 219 subjects, both products are concluded as safe for daily use.

In addition to observed reductions in the clinical endpoints, the proportion analysis also was indicative of a consistent trend, with the DCS powered toothbrush exerting more pronounced effects compared to OBG. For all clinical measures evaluated here, the percent of subjects with reductions greater than 0.3 was statistically significantly higher for DCS compared to OBG.

A clinical recommendation to transition a patient from manual to powered tooth brushing is often done with the intent that such a transition will aid patients in improving efforts to remove plaque. In doing so, the clinical expression of gingivitis is also expected to improve. Indeed, there are a number of studies that support this perspective, reporting that powered tooth brushing is more effective than manual tooth brushing in reducing plaque and gingivitis.[27-30] Overall, the rationale is that improved plaque control through compliance, ease of use, and powered brush head motion features on these devices help to establish and maintain a more health-associated biofilm, thus reducing the inflammatory response in the host.

In the current study, all clinical markers improved for each powered toothbrush following the six-week home use period. As the eligibility profile included habitual manual toothbrush users, it is reasonable to conclude that these outcomes continue to support the view that powered tooth brushing can be more effective than manual brushing. That said, among the two products evaluated here, there appears to be an incremental benefit to users of the DCS product, where high-frequency, high-amplitude brush head movement and a brushing procedure that targets the gumline was significantly better at improving all clinical measures.

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Conflict of Interest and Sources of Funding Statement: F. Mirza, K. Argosino, M. Ward, and San-San Ou are employed by Philips Oral Healthcare.

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A Randomized Parallel Study to Compare the Effects of Powered and Manual Tooth Brushing on Gingival Health and Plaque

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Abstract

- **Objective**: To compare the effect of powered and manual tooth brushing on plaque and gingivitis following two and six weeks of home use.
- **Methods:** This was a randomized, three-arm, parallel-design clinical trial. Eligible participants were manual toothbrush users who were generally healthy non-smokers, aged 18–65 years, with a plaque score of ≥ 1.8 per Lobene and Soparkar Modified Plaque Index (MPI), and mild to moderate gingivitis, defined as a Gingival Bleeding Index (GBI) ≥ 1 on at least 20 sites. Subjects with advanced periodontal disease, excessive gingival recession, and heavy deposits of calculus or rampant decay were excluded. Enrolled participants were randomly dispensed one of three devices: a powered toothbrush (Philips Sonicare DiamondClean Smart with Premium Gum Care brush head) used in either Gum Heath mode (DC-GH) or Clean mode (DC-C), or an ADA reference manual toothbrush (MTB). Efficacy and safety variables were assessed at Baseline, and at two and six weeks following twice-daily product home use.
- **Results:** For the primary endpoint, reduction in gingivitis per Modified Gingival Index (MGI) at Week 2, 188 subjects completed and were included in the analysis. Expressed as percent reduction from Baseline, the adjusted mean reduction and Standard Error (SE) estimates were 60.31% (1.95%) for DC-GH, 53.08% (1.95%) for DC-C, and 16.59% (1.96%) for MTB. The difference between each power toothbrush group and the manual toothbrush was statistically significant ($p < 0.0001$). Statistically significant differences were also observed between DC-GH, DC-C, and manual tooth brushing for MGI at Week 6, as well as for MPI and GBI at Weeks 2 and 6.
- **Conclusion:** The powered toothbrush, used in either Gum Health or Clean mode, was statistically significantly superior to a manual tooth brush in reducing gingival inflammation, gingival bleeding, and plaque following two and six weeks of home use.

(J Clin Dent 2019;30(Spec Iss A)A16–23)

Introduction

The clinical observation of gingivitis is the symptomatic expression of disease that has its origin in factors that happen well upstream of the observation. It can begin simply with plaque biofilm that accumulates on tooth surfaces over a protracted period of time.[1-3] As plaque accumulates, the microbial ecology of the local environment shifts in character, and these shifts elicit a communal synergy in the biofilm matrix that can enable or promote a dysbiotic and pathogenic environment.[4] Indeed, changes in the compositional status of oral microbial communities have been observed across the spectrum of periodontally healthy and diseased patients,[5] with a number of microbial species routinely observed in the presence of disease-affected tissue.[6,7] The constituent speciation profile of these microbial communities can have an effect on treatment outcomes when periodontal disease does occur.[8,9]

Whereas the initial patient response to these complex shifts in a developing periodontopathic biofilm may occur sub-clinically, with measurable changes in the host's expression of inflammatory mediators present in gingival crevicular fluid,[10] the first macroscopic expression of an inflammatory state is gingivitis; that is, edematous, discolored, or bleeding gingival tissue. This is an important symptomatic stage for the patient, as it can be transient. With adequate intervention and treatment, gingival tissue can be restored to a healthy state. However, if left untreated, disease may progress, leading to significant damage to the periodontium, putting the tooth at risk of loss.[11]

It is with this perspective that the utility of everyday plaque removal becomes more than a mundane hygienic habit. Consistent, regular, and thorough plaque removal from tooth surfaces can help stave off an inflammatory state of the gingivae. Further, the mounting body of scientific work that associates an inflammatory oral environment with other systemic diseases or metabolic syndromes exhibiting inflammatory characteristics[12-16] emphasizes the importance of preserving gingival health.

Enabled by mechanization, human factors design, engineering, and digitization, powered oral hygiene cleaning devices continue to evolve in order to aid the user in optimizing their daily oral hygiene. The current clinical study was conducted to evaluate the clinical effects of use of a high-frequency, high-amplitude sonic powered tooth brushing device, used in either "Gum Health" or "Clean" mode, compared to a standard-of-care regimen of manual tooth brushing following a period of product home use. Subjects included in this study had existing levels of mild-to-moderate gingivitis, thus to provide outcomes that may be generalized to a population exhibiting clinically symptomatic levels of disease, where effective hygiene management strategies may help stave off the pathogenic transition from gingivitis to periodontal disease.

Materials and Methods

Study Design and Objectives

This was a prospective, randomized, parallel, single-blind clinical trial conducted in generally healthy volunteers. The study was reviewed and approved by an accredited Institutional Review Board (IRB00007024; Miami, FL, USA). Enrolled subjects were randomized in a 1:1:1 allocation to one of three treatment groups:

- Philips Sonicare DiamondClean Smart powered toothbrush (Philips Oral Healthcare, Bothell, WA, USA) used with Premium Gum Care brush head in Clean Mode (DC-C); two-minute brushing;
- Philips Sonicare DiamondClean Smart powered toothbrush used with Premium Gum Care brush head in Gum Care mode (DC-GH); two-minute brushing plus an additional 20 seconds of brushing per molar sextant;
- ADA reference manual toothbrush (MTB); flat-trim, nylon bristles.

All products were used with a standard fluoride-containing dentifrice, twice daily. After enrollment, subjects were asked to return following two weeks and six weeks of product use at home. At each study visit, subjects were required to present with 3–6 hours of plaque accumulation. Figure 1 provides a flow diagram of study visits and the procedures at each visit.

The primary objective of the study was to compare the effect of the powered toothbrush used in Gum Health Mode to an ADA reference manual toothbrush on the reduction of gingivitis, as measured with the Modified Gingival Index (MGI) following a two-week home use period.

Secondary objectives included comparisons between each power toothbrush group to the manual toothbrush group on the reduction of MGI following six weeks of home use, and the reduction of surface plaque (MPI) and gingival bleeding (GBI) following two and six weeks of product home use, as well as a characterization of the proportion of subjects with improved gingivitis (MGI and GBI) at each time point and the safety of the test products.

Efficacy and Safety Measurements

There were three efficacy endpoint measures in this study. These included the Lobene and Soparkar Modified Plaque Index,[17,18] the Modified Gingival Index,[19] and the Gingival Bleeding Index.[20] Table I provides a depiction of the scoring methodology for each index. In order to minimize bias, the study examiners were blinded to the treatment assignment of subjects. A single assigned examiner performed the measurement of a given index for all subjects and for all visits, thus eliminating variability due to inter-examiner scoring differences or the requirement for inter-examiner calibration. Intra-calibration of study examiners was previously documented and was above acceptability thresholds.

Safety measures were captured by subject report and by oral tissue exam in clinic. In the event that a subject was deemed at greater risk for sustaining an adverse event as a result of study product use or an intercurrent illness or injury during the course of the study, the investigator was able to remove the subject as warranted by clinical judgement.

Study Subjects

Eligible subjects were 18–65 years of age, non-smokers, in generally good health, habitual manual toothbrush users who were able to voluntarily provide informed consent for study participation. Subjects were to have a minimum average plaque score of ≥ 1.8 per the MPI following a 3–6-hour plaque accumulation period, and a Gingival Bleeding Index of ≥ 1 on at least 20 sites. Subjects were not eligible in the event of rampant decay, advanced periodontal disease, gingival recession, heavy deposits of supragingival or subgingival calculus, the presence of a medical or dental contraindication which could be unduly affected by participation in the study, the use of antibiotics within four weeks of enrollment, or use of prescription-dose anti-inflammatory or anti-coagulant medications. Dental students, dental professionals, or persons employed by dental products or dental research entities were not eligible to participate. The use of any other supplementary oral hygiene or tooth bleaching procedures was prohibited during the six-week study period. Compliance to the prescribed regimen and study requirements was tracked by dispensing of a home diary to subjects, and subject interview in clinic.

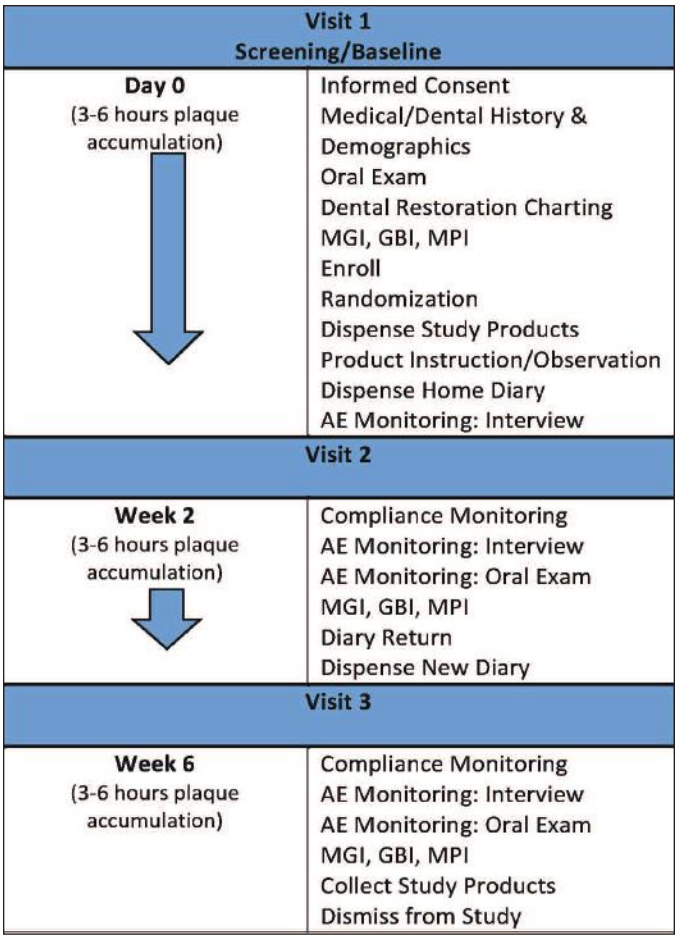

Figure 1. *Study procedures and timelines.*

Data Collection and Data Quality

This study was conducted at a single oral health research site (Salus Research, Ft. Wayne, IN, USA). Study data were collected on a web-based electronic data capture (EDC) system. Access to, and use of the system, was controlled based on the role of the user, thus to maintain the study blind. The clinical site utilized paper source document forms where necessary. Data quality safeguards included programmed logic and edit-checks in the EDC system, as well as remote and on-site data-monitoring by the study project manager.

Table I
Scoring Methodology for Efficacy Metrics: Plaque, Gingival Inflammation and Gingival Bleeding

Lobene and Soparkar Modified Plaque Index, Six Sites per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**4**	**5**
No plaque	Separate flecks of plaque at the cervical margin	A thin continuous band of plaque (up to 1mm) at the cervical margin of the tooth	A band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth	Plaque covering at least 1/3 but less than 2/3 of the crown of the tooth	Plaque covering 2/3 or more of the crown of the tooth
Modified Gingival Index, Four Sites per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**4**	**N/A**
Absence of inflammation	Mild inflammation, slight change in color, little change in texture of the marginal or papillary gingival unit	Mild inflammation but involving the marginal or papillary gingiva	Moderate inflammation; glazing, redness, edema and/or hypertrophy of marginal or papillary gingiva	Severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingiva, spontaneous bleeding, congestion or ulceration	
Gingival Bleeding Index, Four Sites per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**N/A**	**N/A**
No bleeding	Bleeding on gently probing	Bleeding appears immediately upon gently probing	Spontaneous bleeding which is present prior to probing		

Randomization and subject instruction on device use was performed by designated unblinded study personnel. These personnel did not perform any evaluations or assessments related to study endpoints.

Statistical Methods

Sample Size Determination. In prior power versus manual toothbrush studies with an MGI endpoint at Week 2 and a similar population with a plaque accumulation period of 3–6 hours, the difference between the two products for MGI reduction ranged from 0.43 to 0.73, with the standard deviation (SD) range from 0.26 to 0.36. Expressed as percent reduction difference, the range was 23–34%, with an SD range from 12–18%.

For the plaque reduction endpoint (MPI) in these prior studies, the difference between products at Week 2 ranged from 0.41 to 1.36, with an SD range of 0.33–0.66; the percent reduction ranged from 15–48% with the SD range from 12–21%.

Therefore, for the current study, it was assumed that a minimum difference of 0.25 in MGI was sufficient to differentiate either power toothbrush group from the manual toothbrush group, with a common SD of 0.45. A sample size of 60 subjects in each group would allow for approximately 80% power to detect differences using a two-sided t-test, with a 0.05 significance level, after adjusting for multiple comparisons. Similarly, this sample size would allow for detection of at least a 10% difference in percent reduction in MGI between the power and manual tooth brushing treatments, assuming that the common SD was less than 15%. This would also allow for more than 80% power to detect a difference of at least 0.25 in MPI reduction between the power and manual toothbrushes, with a common SD of approximately 0.4 using a two-sided t-test with a 0.05 significance level.

General Considerations

Descriptive statistics were summarized for all variables by treatment group and overall. The statistics for continuous variables included number of observations, mean, median, standard deviation, minimum, maximum, and 95% confidence interval (CI) of the mean. For categorical variables, number and percentage of subjects with the event were presented. All analyses were conducted using SAS® software (Cary, NC, USA).

There was no planned interim analysis for this study, nor were there any pre-defined stopping rules as the risk-profile and potential harms of the products used by subjects on this trial were low.

Efficacy Analysis

The efficacy measures for this study were the reduction in gingival inflammation measured by MGI, the reduction in gingival bleeding measured by GBI, and the reduction in plaque measured by MPI, from Baseline to Week 2 and Week 6.

Three summary scores for each index were calculated for the whole mouth for each subject. These summary scores included: the average score at each visit, calculated as the sum of scores of all evaluable sites divided by the number of evaluable sites; the reduction from Baseline at each follow-up visit, calculated as the Baseline average score minus the post-Baseline average score; and the percent reduction from Baseline at each follow-up visit, calculated as the reduction from Baseline divided by the Baseline average score X 100.

Boxplots were presented to show the distribution of the average score of each index at each study visit for both treatment groups. The least square mean (LSM), the standard error (SE), and the two-sided 95% CI of the mean for the three summary scores were estimated for each treatment group at each visit using a separate ANOVA model for each index, adjusting for the Baseline average score as a covariate. The two-sided 95% CI for the mean difference between the treatment groups was also constructed.

In addition, the proportion (and 95% CI) of subjects with improved gum health, as measured by MGI and GBI, post-two and six weeks of product home use, was also presented. Subjects were defined as having improved gum health at Week 2 and/or Week 6 if their respective reductions in MGI or GBI scores at these visits were greater than or equal to 0.1, or 20% (responder). Subjects with less than 0.1 reduction in MGI or GBI score were defined as not having improved gum health (non-responder). A Fisher's exact test was used

to compare the proportions of responders between the treatment groups.

Results

A total of 209 subjects were screened for this study, with 190 enrolled and randomized. Two were lost to follow-up and 188 completed the study. Among the 188 subjects, 63 in the DC-GH group, 63 in the DC-C group, and 62 in the MTB group were included in all analyses. There were no changes to the analysis plans as described above.

Demographics

The mean age of subjects was 43.6 (SD = 11.9) years, with 72.6% female and 27.4% male participants. There were no statistical differences in the distribution of age and gender of subjects between groups.

Efficacy

Modified Gingival Index (MGI). Figure 2 presents the distributions of the average MGI scores for the three treatment groups at each visit in a boxplot. Table II provides least square (LS) mean MGI score for Baseline and LS mean MGI reduction and percent reduction from Baseline to Week 2 and Week 6, and the proportion of responders in each treatment group.

For the primary efficacy endpoint following two weeks of product use, the LS mean (95% CI) MGI reductions were 1.48 (1.38, 1.57) for DC-GH, 1.30 (1.20, 1.39) for DC-C, and 0.43 (0.33, 0.52) for MTB. Expressed as percent reduction from Baseline, this was 60.31% (56.47%, 64.15%) for DC-GH, 53.08% (49.24%, 56.92%) for DC-C, and 16.59% (12.71%, 20.46%) for MTB.

Following six weeks of product use, the LS mean (95% CI) MGI reductions were 1.46 (1.36, 1.57) for DC-GH, 1.38 (1.28, 1.48) for DC-C, and 0.60 (0.50, 0.70) for MTB. Expressed as percent reduction from Baseline, this was 59.59% (55.54%, 63.64%) for DC-GH, 56.15% (52.11%, 60.20%) for DC-C, and 24.18% (20.09%, 28.27%) for MTB.

Statistical superiority was observed for each power toothbrush group compared to the MTB group with $p < 0.0001$ at both Week 2 and Week 6.

Table II
Modified Gingival Index, Overall, at Baseline, Week 2, Week 6

Variable	Statistic	[d]DC-GH (N=63)	DC-C (N=63)	MTB (N=62)	p-value[a]
Baseline (Day 0)	LS Mean (SE)	2.50 (0.04)	2.49 (0.04)	2.44 (0.04)	0.5481
	95% CI	(2.42, 2.58)	(2.42, 2.57)	(2.36, 2.52)	
			Reduction from Baseline		
Week 2	LS Mean (SE)	1.48 (0.05)	1.30 (0.05)	0.43 (0.05)	<0.0001
	95% CI	(1.38, 1.57)	(1.20, 1.39)	(0.33, 0.52)	
	Diff[b] LS Mean (SE)	1.05 (0.07)	0.87 (0.07)		
	Diff 95% CI	(0.90, 1.20)	(0.72, 1.02)		
	p-value[c]	<0.0001	<0.0001		
Week 6	LS Mean (SE)	1.46 (0.05)	1.38 (0.05)	0.60 (0.05)	<0.0001
	95% CI	(1.36, 1.57)	(1.28, 1.48)	(0.50, 0.70)	
	Diff[b] LS Mean (SE)	0.87 (0.07)	0.78 (0.07)		
	Diff 95% CI	(0.70, 1.03)	(0.62, 0.94)		
	p-value[c]	<0.0001	<0.0001		
			Percent Reduction from Baseline		
Week 2	LS Mean (SE)	60.31 (1.95)	53.08 (1.95)	16.59 (1.96)	<0.0001
	95% CI	(56.47, 64.15)	(49.24, 56.92)	(12.71, 20.46)	
	Diff[b] LS Mean (SE)	43.72 (2.77)	36.49 (2.77)		
	Diff 95% CI	(37.55, 49.89)	(30.33, 42.66)		
	p-value[c]	<0.0001	<0.0001		
Week 6	LS Mean (SE)	59.59 (2.05)	56.15 (2.05)	24.18 (2.07)	<0.0001
	95% CI	(55.54, 63.64)	(52.11, 60.20)	(20.09, 28.27)	
	Diff[b] LS Mean (SE)	35.41 (2.92)	31.97 (2.92)		
	Diff 95% CI	(28.90, 41.92)	(25.47, 38.48)		
	p-value[c]	<0.0001	<0.0001		
			Proportion of Subjects with Improved Gum Health		
Week 2	RFB[e]>=0.1	63 (100%)	63 (100%)	49 (79.0%)	<0.0001
	PRFB[f]>=20%	62 (98.4%)	61 (96.8%)	22 (35.5%)	<0.0001
Week 6	RFB[e]>=0.1	63 (100%)	63 (100%)	56 (90.3%)	0.0011
	PRFB[f]>=20%	62 (98.4%)	61 (96.8%)	31 (50.0%)	<0.0001

Modified Intent to Treat (MITT) population includes all randomized subjects with baseline and Day 14 gingivitis evaluations.
Note: Reduction and percent reduction refers to change from pre to post-treatment.
ANOVA Model for Baseline (Pre-Treatment): Result=Treatment + error.
ANOVA Model for Post-baseline: Outcome = Baseline Result + Treatment + error.
[a]p-value for LSM is based on a fixed effects ANOVA model F-test (Ho: All treatments are equal); p-value for proportion is based on the Fisher's Exact test
[b]Diff = Mean (SE) of the treatment difference relative to MTB.
[c]Dunnett's test P-value, for multiple comparisons. Each treatment is compared to MTB
[d]DC-GH = DiamondClean Smart with Gum Health mode; DC-C = DiamondClean Smart with Clean mode
[e]RFB = Reduction from Baseline
[f]PRFB = Percent Reduction from Baseline

Gingival Bleeding Index (GBI). Figure 3 presents the distributions of the average GBI scores for the three treatment groups at each visit in a boxplot. Table III provides LS mean GBI score for Baseline, and LS mean GBI reduction and percent reduction from Baseline to Week 2 and Week 6, and the proportion of responders in each treatment group. Following two weeks of product use, the LS mean (95% CI) GBI reductions were 0.22 (0.20, 0.25) for DC-GH, 0.21 (0.19, 0.24) for DC-C, and 0.05 (0.02, 0.07) for MTB. Expressed as percent reduction from Baseline, this was 61.12% (53.71%, 68.53%) for DC-GH, 57.20% (49.79%, 64.61%) for DC-C, and 7.97% (0.52%, 15.41%) for MTB.

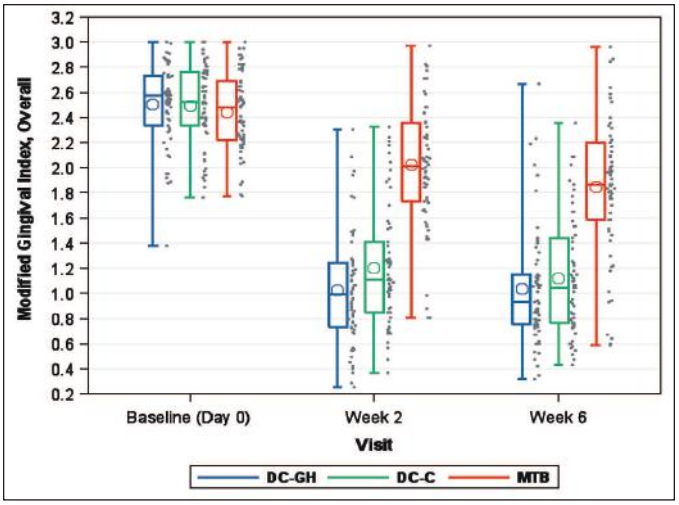

Figure 2. *Boxplot distribution of Modified Gingival Index by visit.*

Following six weeks of product use, the LS mean (95% CI) GBI reductions were 0.21 (0.18, 0.24) for DC-GH, 0.21 (0.17, 0.24) for DC-C, and -0.04 (-0.07, -0.01) for MTB. Expressed as percent reduction from Baseline, this was 57.60% (48.68%, 66.52%) for DC-GH, 53.70% (44.78%, 62.62%) for DC-C, and -10.77% (-19.73%, -1.81%) for MTB.

Statistical superiority was observed between each power toothbrush group compared to the MTB group with $p < 0.0001$ at both Week 2 and Week 6.

Modified Plaque Index (MPI). Figure 4 presents the distributions of the average MPI scores for the three treatment groups at each visit

Table III
Gingival Bleeding Index, Overall, at Baseline, Week 2, Week 6

Variable	Statistic	[d]DC-GH (N=63)	DC-C (N=63)	MTB (N=62)	p-value[a]
Baseline (Day 0)	LS Mean (SE)	0.35 (0.02)	0.39 (0.02)	0.36 (0.02)	0.2997
	95% CI	(0.31, 0.39)	(0.35, 0.43)	(0.32, 0.40)	
			Reduction from Baseline		
Week 2	LS Mean (SE)	0.22 (0.01)	0.21 (0.01)	0.05 (0.01)	<0.0001
	95% CI	(0.20, 0.25)	(0.19, 0.24)	(0.02, 0.07)	
	Diff[b] LS Mean (SE)	0.18 (0.02)	0.17 (0.02)		
	Diff 95% CI	(0.14, 0.22)	(0.13, 0.21)		
	p-value[c]	<0.0001	<0.0001		
Week 6	LS Mean (SE)	0.21 (0.02)	0.21 (0.02)	-0.04 (0.02)	<0.0001
	95% CI	(0.18, 0.24)	(0.17, 0.24)	(-0.07, -0.01)	
	Diff[b] LS Mean (SE)	0.25 (0.02)	0.25 (0.02)		
	Diff 95% CI	(0.19, 0.30)	(0.19, 0.30)		
	p-value[c]	<0.0001	<0.0001		
			Percent Reduction from Baseline		
Week 2	LS Mean (SE)	61.12 (3.76)	57.20 (3.76)	7.97 (3.77)	<0.0001
	95% CI	(53.71, 68.53)	(49.79, 64.61)	(0.52, 15.41)	
	Diff[b] LS Mean (SE)	53.15 (5.32)	49.23 (5.33)		
	Diff 95% CI	(41.29, 65.02)	(37.35, 61.11)		
	p-value[c]	<0.0001	<0.0001		
Week 6	LS Mean (SE)	57.60 (4.52)	53.70 (4.52)	-10.77 (4.54)	<0.0001
	95% CI	(48.68, 66.52)	(44.78, 62.62)	(-19.73, -1.81)	
	Diff[b] LS Mean (SE)	68.37 (6.41)	64.47 (6.41)		
	Diff 95% CI	(54.09, 82.65)	(50.18, 78.77)		
	p-value[c]	<0.0001	<0.0001		
			Proportion of Subjects with Improved Gum Bleeding		
Week 2	RFB[e]>=0.1	57 (90.5%)	57 (90.5%)	22 (35.5%)	<0.0001
	PRFB[f]>=20%	58 (92.1%)	58 (92.1%)	26 (41.9%)	<0.0001
Week 6	RFB[e]>=0.1	53 (84.1%)	53 (84.1%)	10 (16.1%)	<0.0001
	PRFB[f]>=20%	57 (90.5%)	59 (93.7%)	17 (27.4%)	<0.0001

Modified Intent to Treat (MITT) population includes all randomized subjects with baseline and Day 14 gingivitis evaluations.
Note: Reduction and percent reduction refers to change from pre to post-treatment.
ANOVA Model for Baseline (Pre-Treatment): Result=Treatment + error.
ANOVA Model for Post-baseline: Outcome = Baseline Result + Treatment + error.
[a]p-value for LSM is based on a fixed effects ANOVA model F-test (Ho: All treatments are equal); p-value for proportion is based on the Fisher's Exact test
[b]Diff = Mean (SE) of the treatment difference relative to MTB.
[c]Dunnett's test P-value, for multiple comparisons. Each treatment is compared to MTB
[d]DC-GH = DiamondClean Smart with Gum Health mode; DC-C = DiamondClean Smart with Clean mode
[e]RFB = Reduction from Baseline
[f]PRFB = Percent Reduction from Baseline

in a boxplot. Table IV provides the LS mean MPI score for Baseline, and LS mean MPI reduction and percent reduction from Baseline to Week 2 and Week 6 for each treatment group.

Following two weeks of product use, the LS mean (95%) MPI reductions were 0.92 (0.84, 1.00) for DC-GH, 0.75 (0.67, 0.83) for DC-C, and 0.12 (0.04, 0.20) for MTB. Expressed as percent reduction versus Baseline, this was 32.23% (29.43%, 35.03%) for DC-GH, 26.70% (23.90, 29.51%) for DC-C, and 4.07% (1.25%, 6.90%) for MTB.

Following six weeks of product use, the LS mean (95% CI) MPI reductions were 1.10 (1.01, 1.20) for DC-GH, 0.91 (0.82, 1.00) for DC-C, and 0.16 (0.07, 0.26) for MTB. Expressed as percent reduction from Baseline, this was 38.51% (35.35%, 41.67%) for DC-GH, 31.95% (28.79%, 35.11%) for DC-C, and 5.70% (2.51%, 8.88%) for MTB.

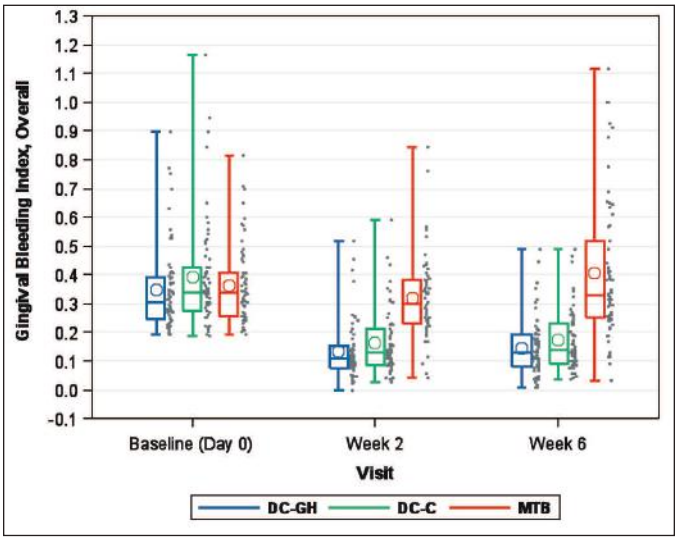

Figure 3. *Boxplot distribution of gingival bleeding index, by visit.*

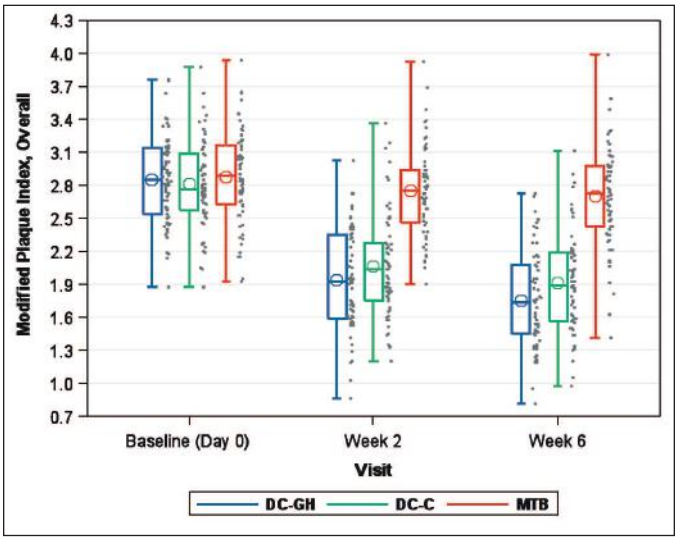

Figure 4. *Boxplot distribution of Modified Plaque Index by visit.*

Table IV
Modified Plaque Index, Overall, at Baseline, Week 2, Week 6

Variable	Statistic	[d]DC-GH (N=63)	DC-C (N=63)	MTB (N=62)	p-value[a]
Baseline (Day 0)	LS Mean (SE)	2.86 (0.05)	2.81 (0.05)	2.88 (0.05)	0.5941
	95% CI	(2.76, 2.96)	(2.71, 2.91)	(2.78, 2.98)	
			Reduction from Baseline		
Week 2	LS Mean (SE)	0.92 (0.04)	0.75 (0.04)	0.12 (0.04)	<0.0001
	95% CI	(0.84, 1.00)	(0.67, 0.83)	(0.04, 0.20)	
	Diff[b] LS Mean (SE)	0.80 (0.06)	0.63 (0.06)		
	Diff 95% CI	(0.67, 0.93)	(0.50, 0.76)		
	p-value[c]	<0.0001	<0.0001		
Week 6	LS Mean (SE)	1.10 (0.05)	0.91 (0.05)	0.16 (0.05)	<0.0001
	95% CI	(1.01, 1.20)	(0.82, 1.00)	(0.07, 0.26)	
	Diff[b] LS Mean (SE)	0.94 (0.07)	0.75 (0.07)		
	Diff 95% CI	(0.79, 1.09)	(0.60, 0.89)		
	p-value[c]	<0.0001	<0.0001		
			Percent Reduction from Baseline		
Week 2	LS Mean (SE)	32.23 (1.42)	26.70 (1.42)	4.07 (1.43)	<0.0001
	95% CI	(29.43, 35.03)	(23.90, 29.51)	(1.25, 6.90)	
	Diff[b] LS Mean (SE)	28.16 (2.01)	22.63 (2.02)		
	Diff 95% CI	(23.67, 32.65)	(18.13, 27.13)		
	p-value[c]	<0.0001	<0.0001		
Week 6	LS Mean (SE)	38.51 (1.60)	31.95 (1.60)	5.70 (1.62)	<0.0001
	95% CI	(35.35, 41.67)	(28.79, 35.11)	(2.51, 8.88)	
	Diff[b] LS Mean (SE)	32.82 (2.27)	26.25 (2.28)		
	Diff 95% CI	(27.75, 37.89)	(21.17, 31.34)		
	p-value[c]	<0.0001	<0.0001		

Modified Intent to Treat (MITT) population includes all randomized subjects with baseline and Day 14 gingivitis evaluations.
Note: Reduction and percent reduction refers to change from pre to post-treatment.
ANOVA Model for Baseline (Pre-Treatment): Result=Treatment + error.
ANOVA Model for Post-baseline: Outcome = Baseline Result + Treatment + error.
[a]p-value for LSM is based on a fixed effects ANOVA model F-test (Ho: All treatments are equal); p-value for proportion is based on the Fisher's Exact test
[b]Diff = Mean (SE) of the treatment difference relative to MTB.
[c]Dunnett's test P-value, for multiple comparisons. Each treatment is compared to MTB
[d]DC-GH = DiamondClean Smart with Gum Health mode; DC-C = DiamondClean Smart with Clean mode

Statistical superiority was observed between each power toothbrush group compared to the MTB group with $p < 0.0001$ at both Week 2 and Week 6.

Safety

Two adverse events to the tongue were reported; one each in each of the power tooth brushing groups. One event was reported as mild and the other as moderate in severity. Both were assessed as possibly related to product use. There were no serious adverse events reported.

Discussion and Conclusions

In a population of subjects with mild to moderate gingivitis, the implementation of a home use, high-frequency, high-amplitude sonic-powered toothbrush was statistically significantly superior to use of a manual toothbrush for all endpoint measures evaluated here: gingival inflammation, gingival bleeding, and surface plaque. These differences were apparent in each of the power toothbrush modes tested, Gum Health and Clean mode. Differentiation between the power and manual tooth brushing groups was observed as early as two weeks, and was sustained following six weeks of use. Both products were regarded as safe for use by the clinical assessor. Within the limits of this study design and its controls, the authors conclude that powered tooth brushing with the Philips Sonicare DiamondClean Smart with Gum Care brush head, used in either Gum Health or Clean mode, is safe and is able to impart a clinically measurable impact on the gingival health and plaque status of subjects compared to manual tooth brushing.

The authors acknowledge that the effect of the interventions tested here occurred within the rigors of a clinical trial setting. This environment implicitly differs from a "real world" scenario. In order to implement the necessary controls that ensure a robust and comprehensive data-set for analysis, applicable procedures, which certainly may modify subject real world behavior, are instituted. That said, such controls are uniformly applied across all treatment groups. Any effects observed in the data analysis as a result should be represented in each of the treatment groups. The observed margin of the differences between products in this trial are indicative that powered brushing can provide incremental oral health benefits to users, even if what is ultimately observed in the clinical setting doesn't precisely mirror the outcomes here.

Powered toothbrushes may provide several advantages for the patient which may, in combination, contribute to these effects. First, the motor that drives brush head motion does so at a frequency that substantially exceeds what can be realistically performed through manual scrubbing. Second, the guidance and timing features of powered toothbrushes help ensure both a thorough and a complete brushing encounter. Third, the power brushing user interface is designed to be easy. The patient has only to place the brush head along the gingival margin and gently glide it across the dentition, with no specific handling maneuvers or dexterity requirements necessary.

It is important to note that the population of subjects included in the study exhibited at least mild clinically observable gingivitis, with at least moderate levels of surface plaque following a reasonably short plaque re-growth period (3–6 hours). In disrupting biofilm and reducing the plaque burden, the study outcomes showed that gingivitis can be effectively treated following the introduction of powered tooth brushing. As the progression of an inflammatory gingival state to periodontal disease can require costly and lengthy professional intervention, and can contribute to complications or elevated risks related to the management of other systemic diseases,[21] the partnership between the dental professional and the patient is crucial in this mild-to-moderate stage of the management of gingivitis. With adequate education and coaching to understand that efforts aimed at prevention of progression, combined with the right home care tools, the patient has the opportunity to be successful in achieving and managing oral health.

This is readily evident in an examination of the proportional analysis completed in this study. For both metrics used to assess gingival health, MGI and GBI, the proportion of subjects in the power toothbrush groups who improved by a margin of at least 20% compared to Baseline, was, at minimum, 90% of subjects as early as Week 2, persisting at or above this level until study completion at Week 6. This is in contrast to the manual toothbrush group, where the highest comparable value was observed as 50.0% of subjects at Week 6 for the MGI endpoint only.

A prior study[22] was conducted to evaluate plaque removal comparisons between power and manual toothbrushes as a function of brushing time. In that study, product use was professionally applied by quadrant (per randomization) and plaque assessments were recorded by a single examiner over consecutive intervals at 10, 20, 30, 45, 60, and 90 seconds (Note: in this study model, 30 seconds of quadrant brushing was, thus, equivalent to a two-minute whole mouth brushing). The outcomes of that study showed that mean plaque scores reduced, and the mean number of plaque-free sites increased over the 90-second brushing period for all toothbrushes evaluated. Looking at the magnitude of plaque reduction benefits, the study showed that the most marked reductions occurred by the 30-second interval (the two-minute brushing equivalent). While plaque levels continued to decline after 30 seconds, the magnitude overall was less pronounced. By looking at a sub-region analysis, however, it was noted that longer brushing duration was needed for "hard-to-reach" posterior interproximal sites to experience similar levels of plaque reduction as easily accessed sites, such as anterior dentition.

The collection of gingivitis metrics was outside the scope of the above study, as observations were collected in-office under highly controlled brushing conditions (professionally applied) so as to remove variability by user habits and dexterity. As such, the translation of plaque removal to gingivitis reduction benefits could only be inferred.

The current study, therefore, enabled an opportunity to pilot the association of plaque removal and associated gum health benefits as they relate to brushing duration (DiamondClean Gum Health mode is three minutes 20 seconds, Clean mode is two minutes). This may be particularly important for patients with hard-to-reach or trouble spots that retain plaque, creating sites of recalcitrant inflammation. Such sites are typically in the posterior regions of the oral cavity, and the Gum Health mode was designed to prompt patients to spend more time in these areas. For each of the study metrics (MPI, GBI, and MGI) there does appear to be a consistent trend suggesting an outcomes benefit for longer brushing duration. For example, at Week 6 the percent reduction (CI) for MPI is 38.51% (35.35, 41.67) for Gum Health mode, and 31.95% (28.79, 35.11) for Clean Mode (Table IV). This tracks with an accompanying trend in GBI outcomes, where the reduction was 57.60% (48.68, 66.52) for Gum Health mode, and 53.70% (44.78, 62.62) for Clean mode (Table III). It is acknowledged

that additional research, statistically powered to directly compare gum health outcomes as a function of brushing duration, would be required to confirm whether such trends exhibit differences that are statistically significant.

In either powered toothbrush mode of usage, however, this study corroborates recent research,[23,24] a meta-analysis,[25] and a systematic review[26] that show the oral health benefits of use of powered toothbrushes compared to manual tooth brushing. Similarly, the outcomes observed here contribute to the evidence base for high-frequency, high-amplitude power toothbrushes; they are highly effective tools that can have demonstrable effects on plaque reduction and improvements to gingival health.

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Conflict of Interest: E. M. Starke, M. Ward, M. Olson, and S-S Ou are employed by Philips Oral Healthcare. K. Milleman and J. Milleman are employed by Salus Research.

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A Comparison of the Effects of a Powered and Manual Toothbrush on Gingivitis and Plaque: A Randomized Parallel Clinical Trial

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Abstract

- **Objective:** To compare the effect of a powered and a manual toothbrush on gingivitis and plaque following two and four weeks of home use.
- **Methods:** This was a randomized, parallel-design, single-blind clinical trial. Eligible participants were generally healthy non-smoking manual toothbrush users aged 18–65 years, with a plaque score of ≥ 1.8 per Lobene and Soparkar Modified Plaque Index (MPI) following a 3–6 hour plaque accumulation period, and mild to moderate gingivitis defined as a Gingival Bleeding Index (GBI) ≥ 1 on at least 20 sites. Subjects with advanced periodontal disease, xerostomia, excessive gingival recession, uncontrolled diabetes, and heavy deposits of calculus or rampant decay were excluded. Enrolled participants were randomly dispensed either a Philips Sonicare powered toothbrush used with the InterCare brush head (PTB) or an American Dental Association (ADA) reference manual toothbrush (MTB). Efficacy and safety variables were assessed at Baseline, and at two and four weeks following twice-daily product home use. The primary endpoint of the study was reduction of gingivitis per the Modified Gingival Index (MGI) after four weeks of home use.
- **Results:** All 148 randomized subjects (74 per group) completed the study. A statistically significant difference in MGI reduction was observed between the two study groups ($p < 0.001$). The least square (LS) mean and standard error reduction from Baseline was 0.72 (0.04) for the PTB group compared to 0.09 (0.04) for the MTB group. Expressed as percent reduction from Baseline, the LS mean values were 35.77% (2.19%) and 4.22% (2.19%) for PTB and MTB, respectively. Statistically significant differences were also observed for MGI reduction at Week 2, as well as for MPI and GBI reduction at Weeks 2 and 4.
- **Conclusion:** The powered toothbrush was statistically significantly superior to a manual toothbrush in reducing gingival inflammation, gingival bleeding, and plaque following two and four weeks of home use.

(J Clin Dent 2019;30(Spec Iss A)A24–29)

Introduction

Regular mechanical removal of the biofilm that coats tooth surfaces is crucial to preserve and sustain oral health.[1] The simple task of brushing away biofilm helps prevent caries,[2,3] as well as inflammation[4] in the adjacent gingival tissues. The effect of mechanical cleaning disrupts the ability of the bacteria that comprise dental plaque to adhere and organize into a biofilm. This biofilm enables synergistic network associations between bacteria, the genes they express, and their resultant byproducts.[5] The absence of regular mechanical plaque removal can potentiate a dysbiotic and virulent oral biofilm environment.[6,7] Indeed, the clinical expression of diseased oral tissue, such as in periodontitis, has a correspondingly different community microbial profile than that of clinically healthy tissue[8,9]

In 2010, de Oliviera, *et al.*[10] published a study in which it was shown that poor oral hygiene (measured by frequency of tooth brushing of subjects) was observed to associate with an increased risk of cardiovascular disease. This is one of several findings that underscore the potential importance of daily mechanical plaque removal. Not only does it have an effect on local tissues, oral health status may associate more broadly with other co-morbidities.

For example, the presence of periodontal disease has been shown to be independently and significantly associated with the presence or exacerbation of other non-communicable chronic diseases. These include: Type II diabetes,[11] chronic kidney disease,[12] rheumatoid arthritis,[13] and chronic obstructive pulmonary disease.[14] From this perspective, the simple task of regular mechanical plaque removal shifts, underscoring the value of educating patients on the importance of their daily oral hygiene techniques and habits.

There have been many innovations in the oral health space aimed to assist patients to improve the quality of their daily oral hygiene. Powered tooth brushing, for example, has been shown to be more effective than manual tooth brushing at removing plaque and reducing gingival inflammation[15-18] Generally speaking, powered devices are designed to improve each brushing encounter with mechanical and digital features that reduce the opportunities for user error, commonly observed to diminish the quality and effectiveness of manual brushing.

That said, not all powered toothbrushes are equally capable of doing so, and it is only following clinical validation that a recommendation to adopt a powered over a manual tooth brushing regimen should be considered. Thus, the current study was conducted to evaluate the safety and efficacy profile of a Philips Sonicare powered toothbrush with the InterCare brush head, compared to a standard-of-care manual toothbrush control. The study endpoints included

surface plaque removal and the reduction in the symptomatic expression of gingivitis; soft tissue edema and bleeding.

Materials and Methods

Study Design and Objectives

This was a prospective, randomized, parallel, single-blind clinical trial conducted in generally healthy volunteers. The study was reviewed and approved by an accredited Institutional Review Board (US IRB, OHRP-IRB00007024). Eligible subjects were randomized in a 1:1 allocation to one of two oral hygiene treatment groups: power tooth brushing (PTB) in Clean mode with the Philips Sonicare Flexcare toothbrush using the standard size InterCare brush head (Philips, Bothell, WA, USA), or an ADA reference manual toothbrush (MTB), used per subject's usual routine. All products were used with a standard fluoride-containing dentifrice, twice daily. After enrollment, subjects were asked to return following two weeks and four weeks of product use. At each study visit, subjects were required to present with 3–6 hours of plaque accumulation. Figure 1 provides a flow diagram of study visits and the procedures at each visit.

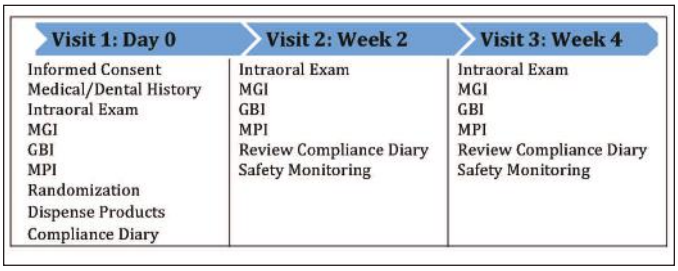


Figure 1. *Study procedures and timelines.*

The primary objective of the study was to compare the effect of use of the powered toothbrush to the ADA reference manual toothbrush on the reduction of gingivitis, as measured by the Modified Gingival Index (MGI), following a four-week home use period.

Secondary objectives included comparisons of reduction in MGI following two weeks of use, and the reduction of surface plaque and gingival bleeding following two and four weeks of product use, as well as a characterization of the safety of the test products.

Efficacy and Safety Measurements

There were three efficacy endpoint measures in this study. These included the Modified Gingival Index,[19] the Gingival Bleeding Index (GBI),[20] and the Lobene and Soparkar Modified Plaque Index (MPI).[21,22] Table I provides a depiction of the scoring methodology for each index. In order to minimize bias, the study examiners were blinded to the treatment assignment of subjects. A single assigned examiner performed the measurement of a given index for all subjects, for all visits, thus eliminating any potential variability due to inter-examiner scoring differences. Intra-calibration of examiner scoring accuracy was previously documented as above acceptability thresholds.

Safety measures were captured by subject diary report of adverse events and by oral tissue exam in the clinic. In the event that a subject was deemed at greater risk for sustaining an adverse event as a result of study product use, or as a result of an intercurrent illness or injury during the course of the study, the study investigator was able to remove the subject, as warranted by clinical judgement.

Study Subjects

Eligible subjects were 18–65 years of age, non-smokers, in generally good health, who were habitual manual toothbrush users that were able to voluntarily provide informed consent for study participation. Subjects were to have a minimum average plaque score of ≥ 1.8 per the MPI following a 3–6 hour plaque accumulation period, and a GBI of ≥ 1 on at least 20 sites. Subjects were not eligible in the event of uncontrolled diabetes, xerostomia, a medical condition requiring antibiotic premedication prior to dental treatment, intercurrent use of prescription-dose anti-inflammatory or antibiotic medications, pregnancy, advanced periodontal disease or gingival recession, or if the subject was a dental student, a dental professional, or a person employed by a dental products or dental research entity.

The use of any other supplementary oral hygiene or tooth bleaching procedures were prohibited during the four-week study period. Compliance to the prescribed regimen and study requirements was tracked by dispensing a home diary to subjects and by interview of study subjects at each study visit.

Table I

Scoring Methodology for Efficacy Metrics: Plaque, Gingival Inflammation and Gingival Bleeding

Lobene and Soparkar Modified Plaque Index, 6 Sites per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**4**	**5**
No plaque	Separate flecks of plaque at the cervical margin	A thin continuous band of plaque (up to 1mm) at the cervical margin of the tooth	A band of plaque wider than 1 mm but covering less than 1/3 of the crown of the tooth	Plaque covering at least 1/3 but less than 2/3 of the crown of the tooth	Plaque covering 2/3 or more of the crown of the tooth
Modified Gingival Index, 2 Sites per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**4**	**N/A**
Absence of inflammation	Mild inflammation, slight change in color, little change in texture of the marginal or papillary gingival unit	Mild inflammation but involving the entire marginal or papillary gingival unit	Moderate inflammation; glazing, redness, edema and/or hypertrophy of margin or papillary unit	Severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingiva, spontaneous bleeding, congestion or ulceration	
Gingival Bleeding Index, 2 Sites per Tooth, Excluding 3rd Molars					
0	**1**	**2**	**3**	**N/A**	**N/A**
No bleeding	Bleeding on gently probing	Bleeding appears immediately upon gently probing	Spontaneous bleeding which is present prior to probing		

Data Collection and Data Quality

This study was conducted at a single oral health research site (Salus Research, Ft. Wayne, IN, USA). Study data were collected on a web-based electronic data capture (EDC) system. Access to, and use of the system, was controlled based on the role of the user, thus to maintain the study blind. The clinical site utilized paper source document forms where necessary. Data quality safeguards included programmed logic and edit checks in the EDC system, as well as remote and on-site data monitoring by the study project manager. Randomization and subject instruction on device use were performed by designated unblinded study personnel. These personnel did not perform any evaluations or assessments related to study efficacy or safety endpoints.

Statistical Methods

Sample Size Determination. In previous similar studies, the observed difference in reduction from Baseline in MGI between a power and manual toothbrush after two and four weeks of home use varied from 0.14 to 0.23, with the pooled standard deviation (SD) ranging from 0.26 to 0.35. When MGI was expressed as percent reduction from Baseline, the differences ranged from 6.4% to 14%, with pooled standard deviation ranging from 12.9% to 16.6%.

Thus, assuming a minimum difference of 0.14 (per MGI) as sufficient to differentiate the two products, and assuming an SD of 0.3, a sample size of 74 subjects in each group (148 subjects overall) would allow for approximately 80% power, using a two-sided t-test with a 0.05 significance level. Similarly, this sample size would allow for approximately 80% power to detect a difference of 6 in the number of bleeding sites (per GBI), assuming an SD of 12, and a difference of 0.20 in plaque reduction (per MPI), assuming a SD of 0.4.

General Analysis Considerations

Continuous variables were summarized using the number of observations, mean, median, standard deviation, and 95% confidence interval (CI) of the mean. Categorical variables were summarized using the frequency, count, and the percentage of subjects in each category. There were no planned interim analyses and no prescribed stopping rules, given the low-risk nature of the products being investigated and short accrual time. All analyses were performed using SAS® software (SAS, Cary, NC).

Efficacy Analysis

The primary efficacy measure for this study was the mean MGI score after four weeks of product use at home. For each subject, the overall MGI score was calculated as the sum of scores for all evaluable sites divided by the number of sites. The overall MGI score was treated as a continuous variable, and was analyzed both as a reduction from baseline and as a percent reduction from Baseline. All efficacy analyses were performed according to the intent to treat principle, with the modification that subjects be excluded in the analysis if they were missing either the baseline or the week 4 MGI score. Similarly, subjects with missing GBI and MPI scores at baseline and or Week 4 were excluded from analyses pertaining to those endpoints.

An analysis of variance model (ANOVA), with the baseline MGI and randomization group as predictors, was used to estimate the least square (LS) mean for MGI score at Week 4 for both treatment groups. Standard errors and 95% CIs for the LSMs were also estimated from this model. Comparisons between the treatment groups were performed using an F-Test.

The secondary efficacy endpoints were analyzed using statistical models similar to the one described above.

Safety Analysis

Safety analyses evaluated clinical oral examination findings (presence of abnormalities in the oral cavity) and adverse events (AE) experienced by the subjects. Oral exam findings were analyzed as the number and percent of subjects with abnormal results, while AEs were listed.

Results

One hundred and fifty-two subjects provided informed consent and were screened for study participation; of these, 148 were randomized (74 subjects per group). All randomized subjects completed the study (Figure 2).

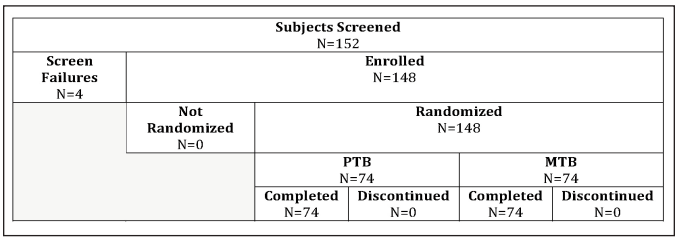


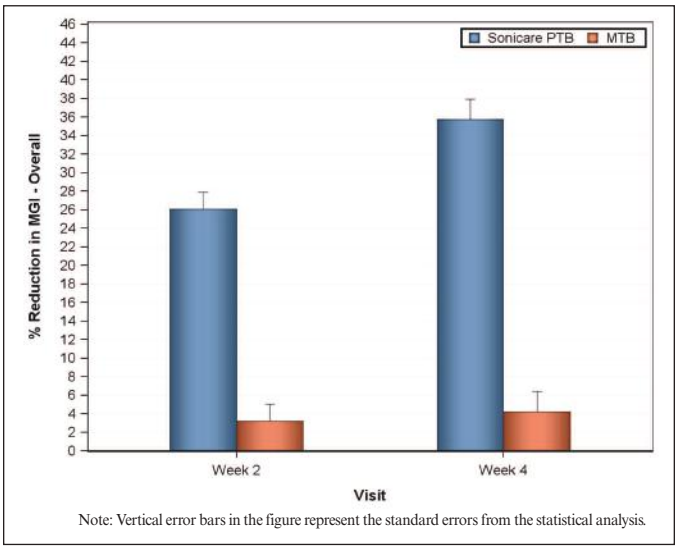
Figure 2. *Subject enrollment and completion metrics.*

Demographics

Of the randomized subjects, the mean age was 42.5 years, with 68.2% female and 31.8% male participants. There were no statistical differences in the distribution of age and gender of subjects between groups.

Efficacy Outcomes

Modified Gingival Index (MGI). Table II provides MGI scores for Baseline, and LS mean MGI reduction and percent reduction from Baseline to Week 2 and Week 4. A depiction of percent reduction from Baseline for each product is provided in Figure 3.



Note: Vertical error bars in the figure represent the standard errors from the statistical analysis.

Figure 3. *Least squares mean, percent reduction from baseline, Modified Gingival Index.*

Table II
Modified Gingival Index, Overall, at Baseline, Week 2, Week 4

Visit	Statistic	Sonicare PTB (N=74)	MTB (N=74)	Treatment Difference	p-value [a]
Baseline MGI Score	LS Mean (SE)	2.00 (0.04)	2.09 (0.04)	-0.10 (0.06)	0.1327
	95% CI	(1.91, 2.08)	(2.00, 2.18)	(-0.22, 0.03)	
Week 2 MGI Score	LS Mean (SE)	1.53 (0.03)	1.97 (0.03)	-0.44 (0.05)	<0.0001
	95% CI	(1.47, 1.60)	(1.90, 2.04)	(-0.53, -0.34)	
Reduction from Baseline to Week 2	LS Mean (SE)	0.51 (0.03)	0.07 (0.03)	0.44 (0.05)	<0.0001
	95% CI	(0.44, 0.58)	(0.01, 0.14)	(0.34, 0.53)	
% Reduction from Baseline to Week 2	LS Mean (SE)	26.11 (1.79)	3.23 (1.79)	22.88 (2.55)	<0.0001
	95% CI	(22.57, 29.65)	(-0.32, 6.77)	(17.85, 27.91)	
Week 4 MGI Score	LS Mean (SE)	1.33 (0.04)	1.96 (0.04)	-0.63 (0.06)	<0.0001
	95% CI	(1.25, 1.41)	(1.87, 2.04)	(-0.75, -0.51)	
Reduction from Baseline to Week 4	LS Mean (SE)	0.72 (0.04)	0.09 (0.04)	0.63 (0.06)	<0.0001
	95% CI	(0.63, 0.80)	(0.00, 0.17)	(0.51, 0.75)	
% Reduction from Baseline to Week 4	LS Mean (SE)	35.77 (2.19)	4.22 (2.19)	31.55 (3.11)	<0.0001
	95% CI	(31.44, 40.11)	(-0.11, 8.55)	(25.40, 37.70)	

[a] p-value is based on an ANOVA model F-test (Ho: Both treatments equal).
Post-Baseline ANOVA Models: Result=Baseline + Treatment + error.

Table III
Number of Sites with Gingival Bleeding Overall, at Baseline, Week 2, Week 4

Visit	Statistic	Sonicare PTB (N=74)	MTB (N=74)	Treatment Difference	p-value [a]
Baseline	LS Mean (SE)	26.46 (1.18)	28.47 (1.18)	-2.01 (1.67)	0.2308
	95% CI	(24.12, 28.80)	(26.13, 30.81)	(-5.32, 1.29)	
Week 2	LS Mean (SE)	13.61 (0.80)	25.54 (0.80)	-11.9 (1.14)	<0.0001
	95% CI	(12.03, 15.20)	(23.95, 27.12)	(-14.2, -9.67)	
Week 4	LS Mean (SE)	13.08 (0.92)	27.40 (0.92)	-14.3 (1.30)	<0.0001
	95% CI	(11.26, 14.89)	(25.58, 29.21)	(-16.9, -11.7)	

[a] p-value is based on an ANOVA model F-test (Ho: Both treatments equal).
Post-Baseline ANOVA Models: Result=Baseline + Treatment + error.

For the primary efficacy endpoint, MGI reduction from Baseline following four weeks of product use, the LS mean (SE) outcomes were 0.72 (0.04) for the PTB and 0.09 (0.04) for the MTB. Expressed as percent reduction from Baseline, this was 35.77% (2.19%) for the PTB and 4.22% (2.19%) for the MTB.

Following two weeks of product use, the LS mean (SE) reduction from Baseline outcomes for MGI were 0.51 (0.03) for the PTB and 0.07 (0.03) for the MTB. Expressed as percent reduction from Baseline, this was 26.11% (1.79%) for the PTB and 3.23% (1.79%) for the MTB.

For MGI, statistically significant differences were observed between the PTB compared to MTB, p-value < 0.0001 at both Week 2 and Week 4.

Gingival Bleeding Index (GBI)

Table III provides GBI outcomes, indicated as the number of bleeding sites for Baseline, Week 2, and Week 4. A depiction of mean reduction of number of bleeding sites from Baseline for each product is provided in Figure 4.

Following two weeks of product use, the LS mean (SE) overall number of bleeding sites was 13.61 (0.80) for the PTB and 25.54 (0.80) for the MTB. Following four weeks of product use, the outcomes were 13.08 (0.92) for the PTB and 27.40 (0.92) for the MTB.

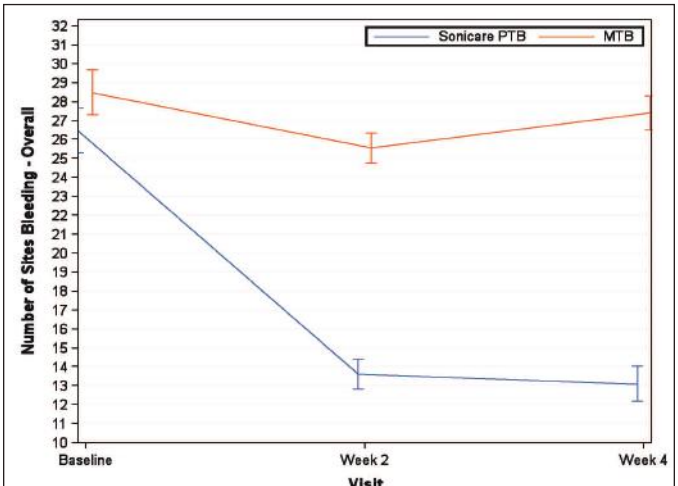
For GBI, statistically significant differences were detected for number of bleeding sites for the PTB compared to the MTB, p-value < 0.0001 at both Week 2 and Week 4.

Modified Plaque Index (MPI)

Table IV provides MPI scores for Baseline and LS mean (SE) MPI reduction and percent reduction from Baseline to Week 2 and Week 4. A depiction of percent reduction from Baseline for each product is provided in Figure 5.

Following two weeks of product use, the LS mean (SE) reduction in MPI was 0.69 (0.04) for the PTB and 0.08 (0.04) for the MTB. Expressed as percent reduction from Baseline, this was 24.82% (1.40%) for the PTB and 2.54% (1.40%) for the MTB.

Following four weeks of product use, the LS mean (SE) reduction in MPI was 0.85 (0.04) for the PTB and 0.00 (0.04) for the MTB.



Note: Vertical error bars in the figure represent the standard errors from the statistical analysis.

Figure 4. *Least Squares mean, number of bleeding sites at Baseline, Week 2, Week 4.*

Table IV
Modified Plaque Index, Overall, at Baseline, Week 2, Week 4

Visit	Statistic	Sonicare PTB (N=74)	MTB (N=74)	Treatment Difference	p-value [a]
Baseline MPI Score	LS Mean (SE)	2.80 (0.04)	2.82 (0.04)	-0.02 (0.06)	0.7193
	95% CI	(2.71, 2.89)	(2.74, 2.91)	(-0.15, 0.10)	
Week 2 MPI Score	LS Mean (SE)	2.13 (0.04)	2.74 (0.04)	-0.61 (0.05)	<0.0001
	95% CI	(2.05, 2.20)	(2.66, 2.81)	(-0.71, -0.51)	
Reduction from Baseline to Week 2	LS Mean (SE)	0.69 (0.04)	0.08 (0.04)	0.61 (0.05)	<0.0001
	95% CI	(0.62, 0.76)	(0.01, 0.15)	(0.51, 0.71)	
% Reduction from Baseline to Week 2	LS Mean (SE)	24.82 (1.40)	2.54 (1.40)	22.28 (1.98)	<0.0001
	95% CI	(22.06, 27.59)	(-0.22, 5.31)	(18.37, 26.19)	
Week 4 MPI Score	LS Mean (SE)	1.96 (0.04)	2.81 (0.04)	-0.85 (0.06)	<0.0001
	95% CI	(1.88, 2.04)	(2.74, 2.89)	(-0.96, -0.74)	
Reduction from Baseline to Week 4	LS Mean (SE)	0.85 (0.04)	0.00 (0.04)	0.85 (0.06)	<0.0001
	95% CI	(0.77, 0.93)	(-0.08, 0.08)	(0.74, 0.96)	
% Reduction from Baseline to Week 4	LS Mean (SE)	30.65 (1.49)	-0.52 (1.49)	31.17 (2.11)	<0.0001
	95% CI	(27.71, 33.60)	(-3.46, 2.43)	(27.00, 35.33)	

[a] p-value is based on an ANOVA model F-test (Ho: Both treatments equal).
Post-Baseline ANOVA Models: Result=Baseline + Treatment + error.

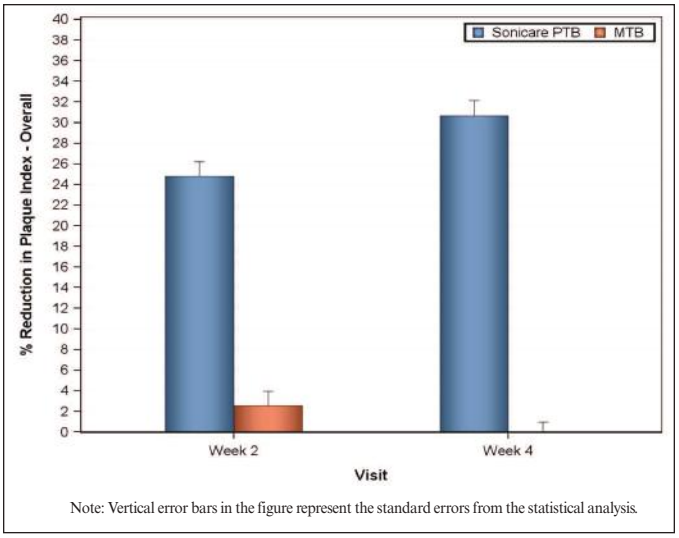


Figure 5. *Least Squares mean percent eduction from baseline for Modified Plaque Index.*

Expressed as percent reduction from Baseline, this was 30.65% (1.49%) for the PTB and -0.52% (1.49%) for the MTB.

For MPI, statistically significant differences were observed between the PTB compared to the MTB, p-value < 0.0001 at both Week 2 and Week 4.

Safety Outcomes

There was one adverse event of "food burn" reported during the study. The event was assessed as mild in severity and unrelated to the study by the investigator.

Conclusion and Discussion

Within the limits and controls of this single-center randomized clinical trial, the powered toothbrush was shown to be statistically significantly superior to the manual toothbrush in reducing gingival inflammation, gingival bleeding, and surface plaque following a period of home use. These differences were observed within the first two weeks of the study, and were sustained upon study completion at Week 4. These outcomes are consistent with prior observations comparing high-frequency, high-amplitude sonic powered toothbrushes with manual toothbrushes on the reduction of plaque and gingivitis.[16-18]

Whereas the outcomes of a straightforward plaque and gingivitis study may seem prosaic in scope, it is, nevertheless, performed with a rigor that recognizes the value of effective oral hygiene. While there are many factors that influence a patient's transition from oral health to disease, specifically to periodontal disease, the transition doesn't happen overnight. Beyond a patient's oral health habits and status, the risk-factor spectrum for periodontitis includes smoking, genetics, nutrition, stress, and other chronic inflammatory conditions[23,24]

From an oral hygiene perspective, however, the first line of defense against developing periodontal disease is plaque removal. In this study, subjects in the power toothbrush group exhibited a rapid reduction in plaque by Week 2, which continued to improve at Week 4. Whereas, only a modest reduction was observed at Week 2 in the manual toothbrush group, and this essentially disappeared by Week 4. This may suggest that manual toothbrush users reverted to their habitual brushing techniques following an initial "on study" period in which, at the onset of the study, additional time and attention may have been given to their brushing routine.

The design and user features of a powered toothbrush help to overcome these engrained habits of manual brushing. Timed quadrant brushing, coupled with high-frequency/high amplitude brush head motion, helps to ensure that patients consistently reach all tooth surfaces in each brushing session. It is also noted that the brushing technique for the powered toothbrush directs users to glide the brush head along the gumline, where plaque accumulates. This is the site of the interface between the host and the dynamic microbiome. As such, thorough mechanical removal of plaque along the gingival margin is a critical aspect of maintaining oral health. The outcomes observed in this trial provide clinical validation that the powered toothbrush tested here effectively does so.

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Conflict of Interest: E. M. Starke, A. Mwatha, M. Ward, K. Argosino, and W. Jenkins are employed by Philips Oral Healthcare. J. Milleman and K. Milleman are employed by Salus Research.

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A Randomized Parallel Study to Assess the Effect of Three Tongue Cleaning Modalities on Oral Malodor

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Abstract

- **Objective:** The objective of this study was to compare the effects of three tongue hygiene regimens on oral malodor.
- **Methods:** This was a single-center, randomized, parallel design study with three treatment groups. Subjects were randomly assigned to perform tongue hygiene with either the Philips Sonicare TongueCare+ BreathRx regimen (STC), Listerine Cool Mint antiseptic rinse (LCM), or tongue brushing with an ADA reference manual toothbrush (MTB). Tooth brushing was standardized for all subjects during the study period, and no other oral or breath hygiene measures were allowed. Eligible subjects met the following criteria: aged 18–70 years, in good general and oral health, non-smoker, with an organoleptic score between 2.7 and 4.5 following a 12–18 hour oral hygiene abstention period. Subjects who had oral appliances or who had periodontal disease or excessive recession were not eligible. The primary endpoint analysis was to evaluate oral malodor based on an organoleptic (OL) score. Additional surrogate measures for oral malodor included quantification of oral hydrogen sulfide (H_2S) level and counts of oral bacteria in secondary analyses. At Day 1, all three malodor endpoints were assessed prior to product use, immediately after use, and four and eight hours after use. Subjects were then provided with instructions on product use at home. Subjects returned to the clinic on Day 8 and the assessments for malodor were repeated for each of the three endpoints, *i.e.*, prior to in-clinic use of the products, immediately after use, and four and eight hours after use.
- **Results:** One hundred sixty-eight (168) subjects were randomized to three groups, with 56 per treatment group. Of these, 165 completed all study visits. Randomized subjects were comparable for baseline characteristics (OL score, age, race, and ethnicity). Overall, oral malodor based on the organoleptic score decreased for all treatment groups at all timepoints. For the primary endpoint, reduction of OL score eight hours following a single product use, the STC regimen reduced malodor per OL score by 46.67% (SE = 2.28%), the LCM value was 22.83% (SE = 2.29%), and MTB was 26.19% (SE = 2.29%). The pair-wise comparisons between STC and each of the treatment groups were statistically significant (p-values < 0.0001). Statistically significant differences were also observed between STC and both LCM and MTB groups in pair-wise comparisons at Day 8 (p-values < 0.0001).
- **Conclusion:** Reductions in malodor were evident following a single use of each product, and also following a seven-day repeat use period. The STC regimen, however, was statistically significantly superior to both LCM and MTB at improving malodor eight hours following the first use. Statistically significant differences in OL scores were sustained between STC and LCM, and STC and MTB at each efficacy timepoint following the seven-day home use period.

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Introduction

Oral malodor is attributed to gaseous metabolites from bacteria in the oral cavity that stream into exhaled breath.[1,2] The tongue, in particular the posterior dorsum of the tongue, is noted as one of the major sites with a high concentration of microbes coating the mucosal surface. This site is implicated as the dominant site of malodor production.[3,4] The metabolites of tongue bacteria can produce volatile sulfur compounds (VSCs), including hydrogen sulfide (H_2S), dimethylsulfide [$(CH_3)_2S$], and methylmercaptan (CH_3SH), which are the main odiferous culprits contributing to halitosis. Oral hygiene, inflammation, and infection[5-7] can affect the character of breath.

The management strategies for reducing oral malodor span a wide range of available medicaments and tools. Oral rinses are commonly used,[8-10] and generally include an antimicrobial ingredient. Mechanical tongue-brushing or tongue-scraping devices[11,12] are also employed to mechanically reduce the overall quantity of bacteria coating the tongue, much like a toothbrush is used to eliminate the surface plaque that coats teeth. In either case, the treatment is targeted to reduce the causative bacteria residing on the tongue, thus reducing the resultant concentration of VSCs as a means to help reduce and control oral malodor.

This study was a randomized and controlled clinical trial initiated to explore whether a two-pronged approach to malodor management (medicament plus tongue cleaning) exhibited any advantages over either rinsing with a medicament alone or to mechanical tongue cleaning alone. In particular, the study evaluated effects on the organoleptic character of breath up to eight hours following a single

use of the assigned product. In this study, only subjects with an existing level of malodor were included.

Surrogate measures for malodor were also included for exploratory purposes. These included assessments of hydrogen sulfide (H_2S), as well as the quantification of both aerobic and anaerobic bacteria following tongue biofilm sampling and culture.

Materials and Methods

Study Design and Objectives

This study was reviewed and approved by the Institutional Review Board of Loma Linda University. All screened and enrolled subjects provided informed consent. The study was conducted according to the ICH Guideline for Good Clinical Practices (GCPs) and the standards of ISO 14155. There were two clinical evaluation days (Day 1 and Day 8), each with four evaluations (prior to in-clinic use of the products, immediately after use, and four and eight hours after use). Table I provides an outline of study visits and the procedures that were performed at each visit. This was a three-arm, single-blind, repeat-measure, parallel-design clinical trial.

Table I
Study Visit Timeline and Procedures

Day 1					Day 8				
• Informed Consent • Medical Dental History • Oral Exam • Randomization • Dispense, Instruct, Use Assigned Product • Provide Compliance Instructions and Diary					• Medical Dental History Update • Collect Compliance Diary • Oral Exam • Product Use • Collect Products • Dismiss				
	Pre	Post	4 Hours	8 Hours		Pre	Post	4 Hours	8 Hours
OL	X	X	X	X	OL	X	X	X	X
H_2S	X	X	X	X	H_2S	X	X	X	X
Micro	X	X	X	X	Micro	X	X	X	X

The primary objective was to compare the reduction in organoleptic scores between three oral malodor treatments eight hours after a single use. Secondary objectives included organoleptic score comparisons at the following timepoints: immediately and four hours following a single use, and then following a one-week period of daily home use, after which organoleptic (OL) scores were taken again in the clinic before, immediately, four, and eight hours following product use.

Similar timepoint comparisons were made between products for the other study surrogate efficacy measures, H_2S, and tongue microbial count (total bacterial load, CFU/cm^2). Safety was also assessed via intraoral examination and per subject report.

Study Subjects

Eligible subjects were male and female adults 18–70 years of age, able to provide informed consent, available to attend study visits, and comply with study procedures. Subjects were non-smokers (defined as use of < 100 cigarettes in their lifetime) with an organoleptic score of 2.7–4.5 following a 12–18 hour oral hygiene abstention period. (Note: the OL score was an average based on the assessment of the three independent judges.) Subjects were not eligible in the event of pregnancy or nursing, a diagnosis of xerostomia, periodontal disease or a dental condition requiring care, Type II diabetes, a gagging reflex that precluded tongue-cleaning, usage of medications known to alter oral flora within one month of study, or the presence of orthodontic brackets or other intra-oral hardware or piercing.

Subjects were required to abstain from the use of any other oral and breath-hygiene products or devices, other than those dispensed for the study. The use of antibiotics or antimicrobials (other than tongue spray or rinse, if assigned) was also prohibited. In the event that a subject required dental care outside the scope of the study, she/he was discontinued.

Prior to each clinical evaluation day (Day 1 and Day 8), subjects were to observe a 12-hour abstention period from alcohol consumption. Subjects also abstained from the application of scented cosmetics, and withheld food and fluid consumption, other than clear liquids, the midnight prior. On study visit days, subjects were provided a standardized meal that did not include foods known to exacerbate oral malodor.

Treatment Groups

Study subjects were randomized to one of the following three tongue-cleaning regimen:

- Tongue brushing with Philips Sonicare TongueCare+ tongue brush used on the Philips Sonicare EasyClean toothbrush handle in Clean mode, with TongueCare+ antimicrobial tongue spray (STC), 20 seconds x 3 (Philips, Bothell, WA, USA);
- Full-mouth rinse with 20 ml Listerine Cool Mint Antiseptic Rinse (Johnson & Johnson, New Brunswick, NJ, USA) for 30 seconds (LCM); or
- Tongue brushing with an ADA reference manual toothbrush (MTB).

After the Day 1 visit procedures were complete, all subjects were provided a standardized at-home tooth brushing regimen. This consisted of the use of a Philips Sonicare EasyClean power toothbrush handle and ProResults brush head in Clean mode, twice daily. Dentifrice was also standardized, with all subjects using Crest® Cool Mint Gel (Procter & Gamble, Cincinnati, OH, USA) for each brushing encounter. Tongue cleaning was performed once daily, in the morning, following tooth brushing.

Randomization, Controls to Minimize Bias, and Data Capture

Randomization was performed by a designated member of the study staff who did not perform any efficacy assessments. Subjects were allocated to a treatment group according to a randomization schedule that was provided to the study site by the sponsor. Approximately equal numbers of subjects, of each gender, were randomized to each treatment group.

In order to minimize bias, the judges performing organoleptic evaluations completed a calibration exercise. This session was conducted with 12 subjects; the intraclass correlation (coefficient [ICC]) for the three judges was 0.901 (95% confidence interval: 0.736, 0.969). Each OL evaluator was blinded to the treatment assignment of each subject, and to the assessments of his/her OL peers. The laboratory personnel performing the microbial counts were also blinded to each subject's treatment assignment.

Study data were collected on a web-based electronic data capture (EDC) system. The system utilized programmed logic and edit-check functions. Access to the EDC system was based on the role of the user (to maintain the study blind), and was protected by log-in identification and password. Source document forms were used by the study site, where necessary. Study staff performed data-quality checks to ensure accuracy of reporting.

Efficacy and Safety Measures

Organoleptic Assessment. Three experienced organoleptic judges were assigned to perform each OL assessment for the duration of the study. All subjects underwent OL assessment, at each timepoint, by each of the three judges. All organoleptic assessments were performed in an examination operatory that preserved the study-blind. A small glass tube was inserted into an aperture in a wall that separated each subject and judge, as well as between the OL judges.

Following product use, and at the assigned time interval, the subject was asked to close his/her mouth for two minutes. Thereafter, a signal prompted the subject to exhale gently through the glass tube. The judge then performed the organoleptic assessment according to the following scale:[13] 0 = odor cannot be detected; 1 = questionable malodor, barely detectable; 2 = slight malodor, exceeds the threshold of malodor recognition; 3 = malodor is definitely detected; 4 = strong malodor; and 5 = very strong malodor. Subjects repeated this procedure three times, once for each OL judge, and they were instructed to keep their mouth closed for two minutes before moving to the next OL judge. The three OL assessments were recorded per subject, and were then averaged.

Hydrogen Sulfide Assessment. Each H_2S assessment was performed with the OralChroma Gas Chromatography device (Nissha Co., Ltd., Schaumburg, IL, USA). This device measures three volatile sulfur compounds. For this study, only H_2S outcomes were collected and reported in parts per billion (ppb).

Oral gas samples were taken using a sterile single-use 1 mL syringe. Subjects inserted the syringe into their mouth with lips closed tightly around the syringe. Subjects were instructed to breathe through their nose for one minute, after which the subject pulled the syringe piston to the end of the syringe, filling the lumen of the syringe with a breath sample. This was released back into the oral cavity and the procedure was repeated, filling the syringe with a second breath sample. This sample was injected into the OralChroma device. The device displayed the results, which were recorded on the study Case Report Form.

Tongue Bacterial Collection and Analysis. The tongue sampling method was based on previously published methods.[14,15] A manual toothbrush (Shaha 5 toothbrush, abcOralCare, Cupertino, CA, USA) was used to collect tongue samples. Each toothbrush was immersed in 70% ethanol for 30 seconds and dried overnight in a sanitized laminar flow hood. At the time of sampling, the brush head was placed on the dorsum of the subject's tongue, 5 cm from the tip, with all bristles in contact with the tongue surface. The brush head was then moved in five gentle oscillations, without bristle movement across the tongue. The brush head was removed and then immediately soaked in a 15 mL sterile centrifuge tube containing ¼-strength 5 mL Ringer's solution. Each tube was labeled with the subject's assigned study ID number.

Each sample was processed within two hours of collection, and kept on ice, or in a 4°C refrigerator, until processing. Samples were vortexed for 30 seconds. For each sample, a 100 µL dilution was plated using an L-shaped rod to evenly spread the inoculum on the surface of an agar plate. Samples were plated in duplicates using a non-selective FAA agar plate (FAA + 7% [v/v] defibrinated horse blood) for aerobes, and a selective FAA agar plate for anaerobes (FAA + 7% [v/v] defibrinated horse blood + vancomycin 2.5 mg/L). Plates were incubated for three days at 37°C for aerobic culture, and seven days at 37°C for anaerobes. Colonies were counted by a blinded laboratory staffer, and recorded in CFU/cm^2.

Safety

Subject safety was assessed by intraoral examination at each study visit, and by subjects' diary report of any adverse experiences occurring at home during the study period.

Statistical Methods

Sample Size Determination. In a previous pilot study,[16] the mean reduction in organoleptic score at six hours post brushing, in subjects using the STC regimen compared to subjects using water only, was 1.6 (SE = 0.13). When compared to subjects who used BreathRx only, the mean reduction in organoleptic score was 1.1 (SE = 0.124).

For the current study, a sample size of 50 subjects per treatment group would provide approximately 80% power to detect a 1.0 difference in the mean OL score between the STC, LCM, and MTB treatment groups, assuming a common standard deviation of 1.5, with a two-sided independent sample t-test with a Dunnett's adjustment for multiple testing (*i.e.*, alpha equal to 0.027).

The remaining efficacy endpoints, H_2S and bacterial counts, were included with no prior pilot study outcomes. As a result, statistical comparisons in the current study were exploratory in nature.

Demographics. Standard subject demographics and baseline characteristics were summarized for all randomized subjects, and for modified Intent-to-Treat (mITT) subject populations. For continuous characteristics, means were compared using one-way analysis of variance (ANOVA). The incidence of the categorical variables was compared using the Chi-square test.

Primary Efficacy Analysis. The primary efficacy measure for this study was the OL score after eight hours of product use, based on assessments provided by three independent, blinded judges. For each subject the organoleptic score was a value obtained by averaging the scores of each of the three independent judges. The primary analysis was performed on a mITT basis; that is, including all subjects with a baseline (prior to the single use of products) and an eight-hour efficacy evaluation. The following hypotheses were evaluated:

- Null Hypothesis H_o: No difference among the three treatment groups; and
- Alternative Hypothesis H_a: At least two of the treatment groups differ.

The analysis was implemented using ANOVA modelling with overall comparisons between the three treatment groups performed using an F-test. If the overall F-test was significant then pairwise differences between STC and each of the two-comparator groups (LCM and MTB) were performed using contrast statements (SAS PROC MIXED), with Dunnett's procedure used to control for multiple comparisons. For the eight-hour outcome, the ANOVA model included the randomized treatment group and baseline OL score as predictor variables. Similar models were constructed to evaluate the four-hour and immediately after treatment timepoints.

Secondary Efficacy and Safety Analysis. Secondary efficacy analyses evaluated the change in OL score at Day 8 following an in-clinic use of the three study products. Similar to Day 1 visits, Day 8 assessments were performed after a 12–18 hour oral hygiene abstention period, with OL assessment performed at the same timepoints as at Day 1, *i.e.*, immediately after in-clinic product use, and at four and eight hours after in-clinic use. However, the difference between Day 1 and Day 8 assessments was that the subjects had been using their assigned products at home for a seven-day period. Secondary efficacy

analysis also evaluated surrogate oral malodor measures (hydrogen sulfide level, aerobic and anaerobic bacteria counts in CFU/cm^2) at both Day 1 and Day 8. Similar ANOVA analyses were used for these outcomes. In these analyses, logarithmic transformations were performed on the hydrogen sulfide and bacterial outcomes.

Safety analyses included clinical oral examination findings (the presence of abnormalities in the oral cavity) and adverse events (AE) experienced by the subjects. Oral examination findings were analyzed as the number and percent of subjects with abnormal results, and AEs were listed.

General Analysis Considerations. For all outcome comparisons, the least squares (LS) mean, Dunnett's adjusted standard error (SE) of the mean, and the two-sided 95% confidence intervals (CI) were presented by treatment group.

Due to the short duration and low-risk nature of this study, there were no pre-defined stopping rules. There were also no considerations for an interim analysis for this study.

Results

There were 214 subjects screened for this study. Of these, 168 subjects were enrolled and randomized, with 77 male and 91 female participants. There was no statistical difference in gender distribution between treatment groups. The mean (SD) age of randomized subjects was 38.9 (14.8) years. Table II provides a depiction of subject screening, enrollment, randomization, and completion.

Table II
Subject Enrollment

Subjects Screened N= 214							
Screen Failures N=46	Enrolled N=168						
	Not Randomized N=0	Randomized N=168					
		STC N=56		LCM N=56		MTB N=56	
		C[a] N=55	D[b] N=1	C N=55	D N=1	C N=55	D N=1

a: completed
b: discontinued

Organoleptic Endpoint Results

Table III provides the analysis results of all organoleptic outcomes.

The primary efficacy objective was OL score reduction at eight hours post first product use at Day 1. For this timepoint, the LS mean (95% CI) organoleptic scores were: 1.70 (1.56, 1.84) for STC; 2.42 (2.28, 2.56) for LCM; and 2.33 (2.19, 2.47) for MTB (overall F-test p-value < 0.0001). The differences between STC and MTB, and STC and LCM, were significant (p-value < 0.0001, for each pair-wise comparison). With OL score expressed as LS mean (95% CI) percent reduction from pre-treatment, the following reductions were estimated: 46.7% (42.18%, 51.57%) for STC; 22.8% (18.31, 27.35%) for LCM; and 26.2% (21.66%, 30.72%) for MTB.

At immediately post-treatment, malodor was lowest in the STC group. The LS mean (95% CI) values were: 1.47 (1.36, 1.59) for STC; 1.57 (1.46, 1.69) for LCM; and 1.67 (1.55, 1.78) for MTB. However, only the STC versus MTB comparison was statistically significant (p-value = 0.0330). With OL score expressed as LS mean (95% CI) percent reduction from pre-treatment, the following reductions were estimated: 53.0% (49.37%, 56.71%); 49.6% (45.90%, 53.28%); and 47.1% (43.40%, 50.79%), for STC, LCM, and MTB, respectively.

At the four-hour post-treatment at Day 1, the STC group continued to have the lowest OL score. The LS mean (95% CI) values were: 1.77 (1.65, 1.90) for STC; 2.05 (1.92, 2.18) for LCM; and 1.94 (1.81, 2.07) for MTB, with the difference between STC and LCM statistically significant (p-value = 0.0062). Expressed as percent reduction from pre-treatment, the estimated LS mean (95% CI) values were: 44.06% (39.89%, 48.23%); 34.22% (30.03%, 38.41%); and 38.37% (34.16%, 42.57%) for STC, LCM, and MTB, respectively.

For organoleptic outcomes at Day 8, the STC treatment group exhibited the lowest OL value throughout the visit. Statistically significant differences (p-value < 0.05) were observed between STC and LCM, and STC and MTB, at each timepoint, immediately post-treatment, as well as four hours and eight hours following product use.

Surrogate Efficacy Endpoint Results

Hydrogen Sulfide. Table IV provides the statistical analysis results of all H_2S outcomes. Each of the treatments exhibited reductions in H_2S compared to the pre-treatment value.

For between-group comparisons of H_2S measurements following a single product use at Day 1, statistically significant differences were observed between STC and LCM at each timepoint (p-values of < 0.0001, = 0.0329, = 0.0073 at immediately, four-, and eight-hours following product use, respectively). A statistically significant difference was observed between STC and MTB only at the immediately post-treatment timepoint (p-value < 0.0001).

At Day 8, statistically significant differences were observed between STC and LCM, as well as STC and MTB, only at the immediately post-treatment timepoint (p-values < 0.0001).

Microbial Counts. Tables V and VI provide the statistical analysis results for the aerobic and anaerobic endpoints. Each of the three treatments exhibited reductions in aerobic and anaerobic counts compared to pre-treatment at Day 1 and Day 8.

For between-group comparisons in the quantification of aerobes following a single product use at Day 1, statistically significant differences were observed between STC and LCM at the immediately post timepoint (p-value = 0.0139), and between STC and MTB at the immediately-post and four-hour timepoints (p-value = 0.0136, and 0.0166, respectively). No differences were detected between treatment groups for anaerobic cultures following Day 1 product use.

At Day 8, for aerobes, statistically significant differences between STC and LCM were observed at each timepoint (p-value = 0.0016 at immediately-post, p-value = 0.0005 at four hours, and p-value = 0.0055 at eight hours). For STC and MTB, significant differences were observed at the immediately post and four-hour timepoints (p-value = 0.0064, and 0.0062, respectively). For anaerobes, the only statistically significant difference detected was between STC and LCM at the Day 8, immediately post timepoint (p-value = 0.0229).

Safety Results

Three adverse events were reported during the study, including a bilateral linea alba, cheek biting, and chipped incisor edges on teeth numbers 8 and 9. The first two occurred in the STC treatment group and were judged as unlikely related to the study by the investigator, while the third occurred in the LCM group and was assessed as

unrelated to the study. All three adverse events were assessed as mild in severity.

Discussion and Conclusions

Within the limits and controls of this study, each of the breath hygiene regimens tested are effective and safe for use. For the primary study objective, OL score eight hours following a single-use of the assigned product, the STC breath hygiene regimen (antimicrobial tongue spray plus powered tongue brushing) was superior to both LCM (rinse alone) and MTB (tongue brushing alone). This difference was not uniformly detected between products at the immediately or four hours post single-use at Day 1. However, statistically significant differences were sustained between STC and LCM, and STC and MTB following the seven-day product use period. Figure 1 illustrates the effect of each regimen on OL outcomes, by visit, at each timepoint. It is noted that the combined-regimen STC group exhibits the lowest OL value throughout.

For the surrogate endpoint, hydrogen sulfide gas chromatography, all three treatment groups exhibited reductions in the pre-treatment value at both Day 1 and Day 8. Evaluating the between-group comparisons, both tongue-brushing treatment groups appear to have a more pronounced effect overall, compared to use of rinse alone, at each study visit. The effect of the STC regimen is both immediate and sustained until eight hours, at both Day 1 and Day 8; whereas, the effect of tongue-brushing with MTB alone does not appear to have an immediate effect on H_2S, but it does show an effect by four and eight hours. This also appears to be the trend exhibited by the LCM treatment group, though to a more modest magnitude. At both Day 1 and Day 8, each of the breath hygiene regimens appear to exhibit the most impact on H_2S at the four-hour timepoint. The depiction of H_2S outcomes is provided in Figure 2.

The detection of an effect on breath as measured by a tongue microbial sample that was cultured under aerobic and anaerobic conditions indicates reductions from pre-treatment for all three treatment groups at both Day 1 and Day 8. For aerobes, intermittent differences between STC and either LCM or MTB were observed following a

Table III
Organoleptic Analysis

	Statistic	STC	LCM	MTB	p-value[a]
Day 1					
Pre-treatment	LS Mean (SE)	3.09 (0.05)	3.16 (0.05)	3.20 (0.05)	0.3602
	95% CI	(2.98, 3.20)	(3.05, 3.27)	(3.09, 3.31)	
	p-value[b]		0.5885	0.2682	
Post-treatment	LS Mean (SE)	1.47 (0.06)	1.57 (0.06)	1.67 (0.06)	0.0592
	95% CI	(1.36, 1.59)	(1.46, 1.69)	(1.55, 1.78)	
	p-value[b]		0.3645	0.0330	
	LS Mean (SE) PRFP[c]	53.04 (1.86)	49.59 (1.87)	47.10 (1.87)	
	95% CI	(49.37, 56.71)	(45.90, 53.28)	(43.40, 50.79)	
4 hours	LS Mean (SE)	1.77 (0.07)	2.05 (0.07)	1.94 (0.07)	0.0123
	95% CI	(1.65, 1.90)	(1.92, 2.18)	(1.81, 2.07)	
	p-value[b]		0.0062	0.1393	
	LS Mean (SE) PRFP[c]	44.06 (2.11)	34.22 (2.12)	38.37 (2.13)	
	95% CI	(39.89, 48.23)	(30.03, 38.41)	(34.16, 42.57)	
8 hours	LS Mean (SE)	1.70 (0.07)	2.42 (0.07)	2.33 (0.07)	<0.0001
	95% CI	(1.56, 1.84)	(2.28, 2.56)	(2.19, 2.47)	
	p-value[b]		<0.0001	<0.0001	
	LS Mean (SE) PRFP[c]	46.67 (2.28)	22.83 (2.29)	26.19 (2.29)	
	95% CI	(42.18, 51.17)	(18.31, 27.35)	(21.66, 30.72)	
Day 8					
Pre-treatment	LS Mean (SE)	2.62 (0.08)	2.95 (0.08)	2.89 (0.08)	0.0082
	95% CI	(2.46, 2.77)	(2.79, 3.10)	(2.74, 3.05)	
	p-value[b]		0.0074	0.0292	
Post-treatment	LS Mean (SE)	1.41 (0.05)	1.95 (0.05)	1.84 (0.05)	<0.0001
	95% CI	(1.31, 1.51)	(1.85, 2.05)	(1.74, 1.93)	
	p-value[b]		<.0001	<.0001	
	LS Mean (SE) PRFP[c]	49.96 (2.03)	28.60 (2.00)	34.82 (1.99)	
	95% CI	(45.96, 53.96)	(24.64, 32.55)	(30.88, 38.75)	
4 hours	LS Mean (SE)	1.75 (0.07)	2.26 (0.07	2.18 (0.06	<0.0001
	95% CI	(34.32, 44.18)	(13.46, 23.21)	(16.20, 25.90)	
	p-value[b]		<0.0001	<0.0001	
	LS Mean (SE) PRFP[c]	39.25 (2.50)	18.34 (2.47)	21.05 (2.46)	
	95% CI	(34.32, 44.18)	(13.46, 23.21)	(16.20, 25.90)	
8 hours	LS Mean (SE)	1.89 (0.07)	2.41 (0.07	2.40 (0.07	<0.0001
	95% CI	(1.75, 2.03	(2.28, 2.55)	(2.26, 2.53	
	p-value[b]		<0.0001	<0.0001	
	LS Mean (SE) PRFP[c]	34.54 (2.66)	12.07 (2.63)	13.57 (2.61)	
	95% CI	(29.29, 39.79)	(6.88, 17.26)	(8.40, 18.73)	

[a] p-value is based on an ANOVA model F-test (Ho: No differences between the 3 treatment groups)
[b] Dunnett's test p-values, for multiple comparisons, each treatment is compared to STC
[c] PRFP = Percent Reduction from Pre-treatment value

Table IV
Hydrogen Sulfide Analysis, Log10 in ppb

	Statistic	STC	LCM	MTB	p-value[a]
Day 1					
Pre-treatment	LS Mean (SE)	2.04 (0.11)	2.03 (0.12)	2.00 (0.12)	0.9575
	95% CI	(1.82, 2.27)	(1.80, 2.26)	(1.77, 2.23)	
	p-value[b]		0.9955	0.9423	
Post-treatment	LS Mean (SE)	0.89 (0.11)	1.81 (0.11)	1.55 (0.11)	<0.0001
	95% CI	(0.68, 1.10)	(1.60, 2.02)	(1.34, 1.76)	
	p-value[b]		<0.0001	<0.0001	
4 Hours	LS Mean (SE)	0.82 (0.12)	1.22 (0.12)	0.87 (0.12)	0.0359
	95% CI	(0.59, 1.05)	(0.99, 1.45)	(0.64, 1.11)	
	p-value[b]		0.0329	0.9345	
8 Hours	LS Mean (SE)	0.92 (0.12)	1.42 (0.12)	1.18 (0.12)	0.0148
	95% CI	(0.68, 1.16)	(1.18, 1.66)	(0.94, 1.42)	
	p-value[b]		0.0073	0.2222	
Day 8					
Pre-treatment	LS Mean (SE)	1.83 (0.13)	2.07 (0.13)	1.75 (0.13)	0.2172
	95% CI	(1.57, 2.09)	(1.81, 2.33)	(1.49, 2.01)	
	p-value[b]		0.3405	0.8850	
Post-treatment	LS Mean (SE)	0.88 (0.10)	1.80 (0.11)	1.56 (0.11)	<0.0001
	95% CI	(0.68, 1.09)	(1.59, 2.01)	(1.36, 1.77)	
	p-value[b]		<0.0001	<0.0001	
4 Hours	LS Mean (SE)	0.80 (0.12)	1.16 (0.12)	0.93 (0.12)	0.1053
	95% CI	(0.56, 1.03)	(0.92, 1.39)	(0.70, 1.17)	
	p-value[b]		0.0654	0.6304	
8 Hours	LS Mean (SE)	1.08 (0.12)	1.33 (0.12)	1.08 (0.12)	0.2447
	95% CI	(0.85, 1.31)	(1.09, 1.56)	(0.84, 1.31)	
	p-value[b]		0.2509	0.9999	

[a] p-value is based on an ANOVA model F-test (Ho: No differences between the 3 treatment groups)
[b] Dunnett's test p-values, for multiple comparisons, each treatment is compared to STC

Table V
Tongue Microbial Sample, Aerobes, Log10 CFU/mL

	Statistic	STC	LCM	MTB	p-value[a]
Day 1					
	LS Mean (SE)	6.65 (0.06)	6.65 (0.06)	6.66 (0.06)	0.9948
	95% CI	(6.54, 6.76)	(6.54, 6.76)	(6.54, 6.77)	
	p-value[b]		0.9999	0.9952	
Post-treatment	LS Mean (SE)	6.07 (0.07)	6.32 (0.07)	6.32 (0.07)	0.0082
	95% CI	(5.94, 6.20)	(6.19, 6.45)	(6.19, 6.45)	
	p-value[b]		0.0139	0.0136	
4 Hours	LS Mean (SE)	6.12 (0.06)	6.29 (0.06)	6.35 (0.06)	0.0235
	95% CI	(6.00, 6.24)	(6.17, 6.42)	(6.23, 6.47)	
	p-value[b]		0.0843	0.0166	
8 Hours	LS Mean (SE)	6.14 (0.06)	6.25 (0.06)	6.29 (0.06)	0.2269
	95% CI	(6.02, 6.26)	(6.12, 6.37)	(6.16, 6.41)	
	p-value[b]		0.3637	0.1716	
Day 8					
Pre-treatment	LS Mean (SE)	6.70 (0.05)	6.67 (0.05)	6.64 (0.05)	0.7131
	95% CI	(6.60, 6.80)	(6.57, 6.77)	(6.55, 6.74)	
	p-value[b]		0.8781	0.6225	
Post-treatment	LS Mean (SE)	6.08 (0.06)	6.36 (0.06)	6.32 (0.06)	0.0013
	95% CI	(5.96, 6.19)	(6.25, 6.47)	(6.21, 6.44)	
	p-value[b]		0.0016	0.0064	
4 Hours	LS Mean (SE)	6.02 (0.06)	6.33 (0.06)	6.27 (0.06)	0.0006
	95% CI	(5.90, 6.14)	(6.22, 6.45)	(6.15, 6.39)	
	p-value[b]		0.0005	0.0062	
8 Hours	LS Mean (SE)	6.15 (0.06)	6.40 (0.06)	6.31 (0.06)	0.0098
	95% CI	(6.03, 6.26)	(6.28, 6.51)	(6.20, 6.43)	
	p-value[b]		0.0055	0.0846	

[a] p-value is based on an ANOVA model F-test (Ho: No differences between the 3 treatment groups)
[b] Dunnett's test p-values, for multiple comparisons, each treatment is compared to STC

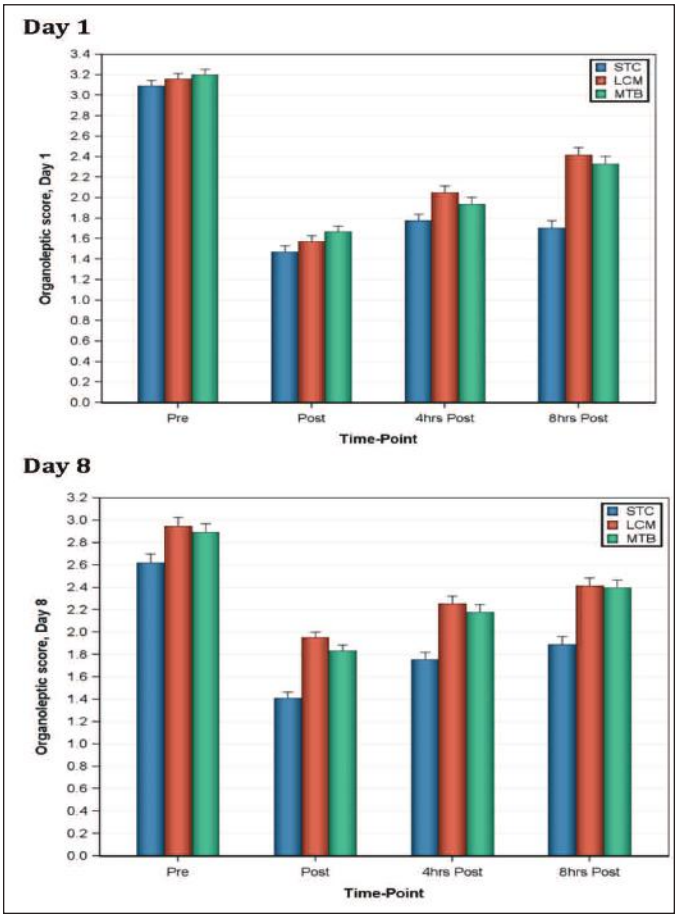

Figure 1. *Least squares mean, organoleptic score.*

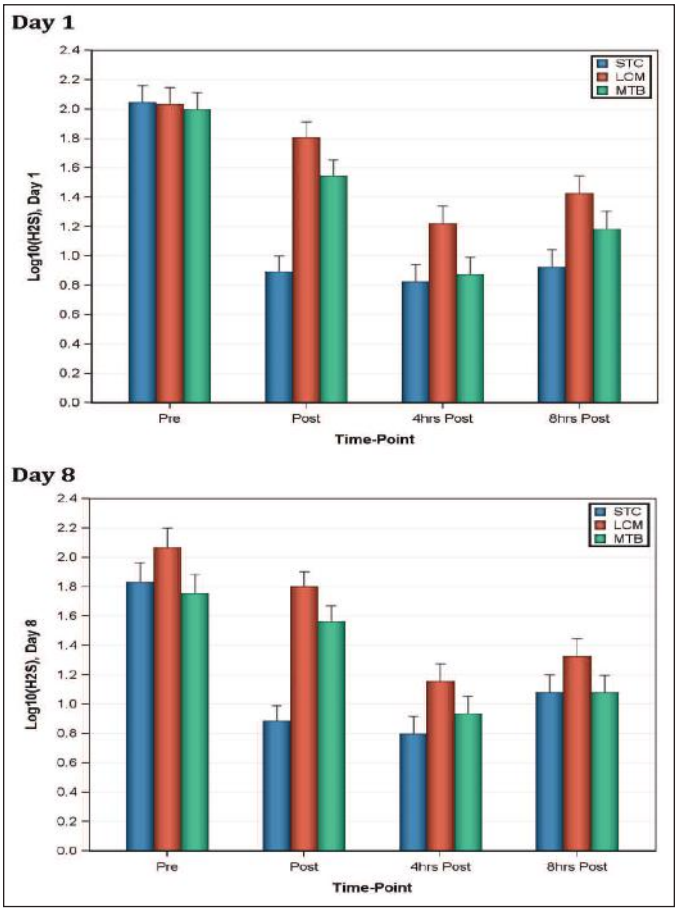

Figure 2. *Hydrogen sulfide, log10 reduction from pre-treatment.*

Table VI
Tongue Microbial Sample, Anaerobes, Log10 CFU/mL

	Statistic	STC	LCM	MTB	p-value[a]
Day 1					
Pre-treatment	LS Mean (SE)	6.63 (0.06)	6.49 (0.06)	6.45 (0.06)	0.1082
	95% CI	(6.51, 6.75)	(6.37, 6.61)	(6.33, 6.57)	
	p-value[b]		0.2104	0.0814	
Post-treatment	LS Mean (SE)	6.13 (0.05)	6.24 (0.05)	6.23 (0.06)	0.2825
	95% CI	(6.02, 6.24)	(6.14, 6.35)	(6.12, 6.34)	
	p-value[b]		0.2389	0.3518	
4 hours	LS Mean (SE)	5.93 (0.07)	6.15 (0.07)	6.00 (0.07)	0.0922
	95% CI	(5.79, 6.07)	(6.01, 6.29)	(5.86, 6.15)	
	p-value[b]		0.0596	0.6967	
8 Hours	LS Mean (SE)	5.85 (0.08)	6.05 (0.08)	5.97 (0.08)	0.1709
	95% CI	(5.70, 6.00)	(5.90, 6.20)	(5.81, 6.12)	
	p-value[b]		0.1098	0.4631	
Day 8					
Pre-treatment	LS Mean (SE)	6.34 (0.06)	6.29 (0.06)	6.25 (0.06)	0.5584
	95% CI	(6.23, 6.46)	(6.18, 6.41)	(6.14, 6.37)	
	p-value[b]		0.7622	0.4539	
Post-treatment	LS Mean (SE)	5.64 (0.07)	5.89 (0.07)	5.80 (0.07)	0.0395
	95% CI	(5.50, 5.78)	(5.75, 6.03)	(5.66, 5.94)	
	p-value[b]		0.0229	0.1873	
4 Hours	LS Mean (SE)	5.44 (0.09)	5.63 (0.09)	5.43 (0.09)	0.2330
	95% CI	(5.26, 5.63)	(5.44, 5.82)	(5.24, 5.61)	
	p-value[b]		0.2686	0.9891	
8 Hours	LS Mean (SE)	5.61 (0.09)	5.71 (0.09)	5.76 (0.09)	0.4860
	95% CI	(5.43, 5.79)	(5.54, 5.89)	(5.58, 5.94)	
	p-value[b]		0.6350	0.3931	

[a]p-value is based on an ANOVA model F-test (Ho: No differences between the 3 treatment groups)
[b]Dunnett's test p-values, for multiple comparisons, each treatment is compared to STC

single product use at Day 1. Statistical differences, however, showed a more general trend at Day 8, with STC statistically different from LCM at all timepoints, and from MTB up to four hours following product use.

The analysis of anaerobic culture outcomes indicates reductions in concentration for all three treatment groups, at each visit. However, it did not indicate statistical dominance for differences between any of the products, though the STC group appears to trend lower throughout.

This study was designed and powered to determine whether organoleptic distinctions could be made between the three regimens. The addition of the H_2S and microbial count endpoints was exploratory in nature and intended to help elicit how each treatment modified oral malodor (by reducing sulfide gas in breath, or by affecting the bacterial ecology of the tongue). Also, they were included to determine whether these additional endpoints tracked with the observed changes in organoleptic score. A cursory look at trends is difficult to interpret. As such, a supplementary correlation analysis was completed in order to evaluate these surrogate endpoints, relative to the organoleptic measure. The r-squared value for OL and H_2S was 0.11; for OL and aerobes, it was 0.10; and for OL and anaerobes, it was -0.09. Similarly, low r-squared values were observed at other timepoints and also between H_2S, aerobes, and anaerobes. In general, neither H_2S nor microbial counts were compelling surrogate markers for organoleptic oral malodor detection in this trial. The use of these measures as surrogates for OL in any subsequent study should be initiated with caution, with the appropriate statistical and population eligibility requirements carefully planned.

As the focus of this study was primarily on organoleptic effects of each regimen up to eight hours following use on a given treatment day, the effect of each regimen following the home use period was not an explicit objective. That said, each of the regimens do appear to have an effect following the seven-day home use period. A cursory look at the pre-treatment value at Day 1 appears different than the pre-treatment value at Day 8. To explore this further, a *post hoc* analysis was completed to evaluate the extent to which statistical differences in OL, following repeat use, may exist. Table VII provides this analysis. In particular, daily use of the tongue-brushing regimens (STC, MTB) appear to be most effective over the seven-day home use period, with STC exhibiting an LS mean (95% CI) reduction of 15.77% (10.91%, 20.64%), and MTB exhibiting an 8.46% (3.50%, 13.32%) reduction. Whereas, reduction over time following use of LCM was 5.49% (0.65%, 10.34%). In this *post hoc* analysis, the difference between STC and LCM was statistically significant (p-value = 0.0069). These over-time effects should be taken into consideration for future study designs. From a patient's point of view, such outcomes may prove to provide a more meaningful gauge of product efficacy, where a steady decline in malodor measures following regular and repeat product use, helps limit cyclical extremes of malodor in a given day, and over a period of days.

An additional observation is with respect to changes in quantification of the microbial population. Reductions were observed for all treatment groups at both Day 1 and Day 8. There have been variable reports of success in assessing the effects of tongue cleaning on the microbial population of the tongue dorsum following introduction of a treatment.[17-19] With its reasonably large sample size and repeated-measures approach, this study does provide some fruitful general evidence to suggest that the microbial population of the tongue is, indeed, altered following intervention. In future studies, additional sensitivities may be gained by including endpoints, and a subsequent correlation exercise, where microbial speciation analysis with PCR, rather than the more general aerobic/anaerobic quantification, is utilized.

It is also noted that this study design necessitated the standardization of the tooth brushing regimen across all treatment groups in order to isolate differences in breath regimens. The selected toothbrush, in this case, was a Sonicare powered toothbrush (PTB). This PTB has previously been demonstrated to reduce gingival inflammation and supragingival plaque in as early as two weeks.[20-22] As oral status, notably plaque and gingivitis, can be potential sources of malodor, it is not possible to determine the extent to which the standardized use of the PTB may have affected the malodor outcomes, in particular, following the seven-day period of use. Going forward, a study design that includes a negative control for both oral and breath hygiene may help elicit these effects. Ideally, plaque and gingivitis endpoints would be assessed in this model, as well.

Overall, a breath hygiene regimen that includes mechanical disruption of the tongue microflora appears to be a more effective approach for patients managing oral malodor than the use of an antimicrobial rinse alone. Combining these techniques – tongue

Table VII
Comparison of Organoleptic Values, Day 1 Pre-treatment to Day 8 Pre-treatment

	Statistic	STC	LCM	MTB	p-value[a]
Day 1					
Pre-treatment	LS Mean (SE)	3.09 (0.05)	3.16 (0.05)	3.20 (0.05)	0.3602
	95% CI	(2.98, 3.20)	(3.05, 3.27)	(3.09, 3.31)	
Day 8					
Pre-treatment	LS Mean (SE)	2.65 (0.07)	2.94 (0.07)	2.87 (0.07)	0.0163
	95% CI	(2.50, 2.79)	(2.80, 3.09)	(2.72, 3.01)	
Reduction, Day 1 to Day 8					
	LS Mean (SE)	0.50 (0.07)	0.21 (0.07)	0.28 (0.07)	0.0163
	95% CI	(0.36, 0.65)	(0.06, 0.35)	(0.14, 0.43)	
	p-value[b]		0.0110	0.0712	
Percent Reduction, Day 1 to Day 8					
	LS Mean (SE)	15.77 (2.46)	5.49 (2.45)	8.46 (2.46)	0.0112
	95% CI	(10.91, 20.64)	(0.65, 10.34)	(3.60, 13.32)	
	p-value[b]		0.0069	0.0690	

[a] p-value is based on an ANOVA model F-test (Ho: No differences between the 3 treatment groups)
[b] Dunnett's test p-values, for multiple comparisons, each treatment is compared to STC

brushing with antimicrobial rinse application – does appear to have the most impactful effect on the organoleptic character of breath. Prior studies [12,23] have also reported improvements in oral malodor using a combined treatment approach, though the small sample size in both of these cited studies and the lack of a comparator in the latter, are noted. The current study, however, was not limited by these constraints, and for patients who suffer from oral malodor this two-pronged approach may provide a more pronounced immediate and, so-called "all-day" (*i.e.*, eight-hour), benefit.

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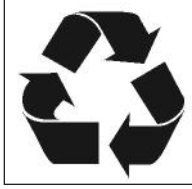

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