Six-Month Evaluation of a Sodium Bicarbonate-Containing Toothpaste for Reduction of Established Gingivitis: A Randomized USA-Based Clinical Trial

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Abstract

- **Objective:** Short-term use of sodium bicarbonate ($NaHCO_3$)-containing toothpaste reduces plaque and improves clinical measures of gingivitis. To examine this over a longer period, we compared efficacy and tolerability of twice-daily brushing for 24 weeks with 67% or 0% $NaHCO_3$-containing toothpastes in USA-based participants with moderate gingivitis (Clinicaltrials.gov:NCT02207400).
- **Methods:** This was a six-month, randomized, examiner-blind, parallel-group, clinical trial. Investigators randomized adults with blood in expectorate after brushing and ≥ 20 gingival bleeding sites to 67% $NaHCO_3$ (n = 123; n = 107 completed study) or 0% $NaHCO_3$ (n = 123; n = 109 completed study) toothpastes. Primary efficacy variables included between-treatment differences in number of bleeding sites and Modified Gingival Index (MGI) score at 24 weeks. Secondary efficacy variables included Bleeding Index and Turesky modification of the Quigley-Hein Plaque Index (overall and interproximal sites) at six, 12, and 24 weeks. A subset of 50 participants underwent sampling to assess plaque microbiology over the course of treatment.
- **Results:** Compared with the 0% $NaHCO_3$ toothpaste, the 67% $NaHCO_3$ toothpaste produced statistically significant improvements at Week 24 in number of bleeding sites (46.7% difference) and MGI (33.9% difference), and for all other endpoints (all $p < 0.0001$). There was no significant between-treatment difference in the proportion of participants harboring opportunistic pathogens. Products were generally well tolerated, with two and five treatment-related adverse events reported in the 67% and 0% $NaHCO_3$ toothpaste groups, respectively.
- **Conclusions:** Gingival bleeding, gingivitis, and plaque indices were significantly improved at six, 12, and 24 weeks with twice-daily brushing with 67% $NaHCO_3$-containing toothpaste in participants with moderate gingivitis.

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Introduction

Around half of adults in the United States have periodontitis,[1] a form of periodontal disease that can ultimately be functionally limiting.[2] Periodontitis is typically preceded by plaque-induced gingivitis,[3] which may be most noted when bleeding occurs upon physical agitation of the gums, such as during tooth brushing or flossing.[4] One of the major etiological factors in gingivitis development is the change in quality and quantity of micro-organisms resident in the polymer matrix that composes the plaque biofilm.[5,6] Removal of plaque by practicing good oral hygiene and undergoing professional dental cleaning is recommended to prevent development of gingivitis and periodontitis.[3,5]

Sodium bicarbonate ($NaHCO_3$; baking soda) can disrupt dental plaque biofilms *in vitro* and reduce the number of micro-organisms that comprise the biofilm without any inherent antimicrobial effect.[7] This disruption may explain beneficial clinical anti-gingivitis effects of a commercially available fluoride toothpaste containing 67% $NaHCO_3$ reported in a series of historical investigations.[8–11] More recently, studies have shown that a single timed brushing with fluoride toothpastes containing between 20% and 67% $NaHCO_3$ exerts a significantly greater effect on plaque removal than commercially available fluoride toothpastes without $NaHCO_3$, including plaque removal from interproximal areas where physical displacement of plaque is challenging.[12-16] In addition, a series of studies in individuals with evidence of blood in the expectorate on brushing have consistently found that twice-daily brushing at home for 12 weeks with a 67% $NaHCO_3$-containing toothpaste produces statistically significant improvements in clinical measures of gingivitis compared with a toothpaste without $NaHCO_3$.[17] However, the longer-term effects of a 67% $NaHCO_3$-containing toothpaste on plaque and gingivitis in individuals with gingival bleeding have yet to be established.

A large number of laboratory and clinical studies have been reported to confirm the overall safety of $NaHCO_3$-containing toothpastes.[18-20] Moreover, $NaHCO_3$ is very low in abrasiveness, which helps prevent increases in tooth sensitivity and is safe for people who require a low salt diet, as it has been reported that between 5% to 7% of toothpaste is swallowed after brushing.[21]

This study evaluated and compared efficacy and tolerability of twice-daily brushing with 67% or 0% $NaHCO_3$-containing toothpastes over 24 weeks in a US-based population with moderate gingivitis at baseline, and evidence of blood in the expectorate or bleeding on brushing. The primary efficacy variables were number of bleeding sites and Modified Gingival Index (MGI) after 24 weeks of use. Secondary efficacy variables were the aforementioned indices at six and 12 weeks, modified Bleeding Index (BI), Turesky modification of the Quigley-Hein Plaque Index (TPI), and interproximal TPI at six, 12, and 24 weeks. In addition, microbiological samples were collected at baseline and six, 12, 24, and 32 weeks for analysis of opportunistic micro-organisms in both treatment groups.

Materials and Methods

A six-month, randomized, examiner-blind, parallel-group, clinical trial was performed at Salus Research, Inc., Fort Wayne, IN, USA. The study protocol was approved by an independent institutional review board (U.S. IRB, Miami, FL, USA; #U.S. IRB 2014SRI/11); study procedures were performed in accordance with the ethical standards of the institutional and national research committee, and with the Helsinki declaration. All participants provided written informed consent prior to screening, demonstrated understanding of the protocol, and were considered willing, able, and likely to comply with all study procedures. The protocol was amended to revise micro-sampling text, and clarify study schedule inconsistencies and selected procedures. Changes did not impact study flow or outcomes. The trial was registered at ClinicalTrials.gov (#NCT02207400).

Participants

Potential study volunteers were recruited from the categorized study site database. Participants were ≥ 18 years, in good general health without any significant/relevant medical or oral/dental abnormalities, with ≥ 20 permanent gradable teeth. At baseline, participants had moderate gingivitis, a positive response to bleeding after brushing, and ≥ 20 bleeding sites (derived from the modified BI[22]). Exclusion criteria included: current active caries; more than three periodontal pockets measuring ≥ 5 mm in depth (full mouth pocket probing at 168 buccal and lingual sites using a 10 mm Williams Probe); excessive calculus that interfered with the gingival bleeding examination; severe oral/gingival or any other medical conditions that could compromise the study or pose participant risk; medical conditions affecting gingival bleeding; restorations in a poor state of repair; or orthodontic appliances. Other exclusion criteria were: pregnancy; breast feeding; intolerance/hypersensitivity to study materials; requirement for prophylactic antibiotics prior to dental therapy or use of antibiotics within two weeks prior to screening or during the study; use of a systemic medication within 14 days of gingival examinations that could affect gingival conditions; use of chewing tobacco products within six months prior to screening; use of any investigational drugs or oral care products, or participation in another clinical trial within 30 days of screening.

Clinical Procedures and Study Products

At screening, eligible participants brushed their teeth in their usual manner for one timed minute using a standard 0% $NaHCO_3$ toothpaste with 1100 ppm fluoride as sodium fluoride (NaF; Colgate® Triple Action; Colgate-Palmolive Co, New York, NY, USA; USA-marketed product) and toothbrush (Oral-B® 35 Soft Standard Toothbrush; Procter & Gamble, Cincinnati, OH, USA; USA-marketed product). Eligible participants, with blood in the expectorate or bleeding when brushing, used the toothpaste and toothbrush provided for 7–14 days at home until the baseline visit.

Prior to the baseline visit, participants abstained from brushing over a 12-hour period (+5 hours, -2 hours). At baseline, one dental examiner performed an oral soft tissue (OST) examination and MGI assessment;[23] another examiner performed a BI assessment.[22] Participants with ≥ 20 bleeding sites were eligible for randomization. Participants then rinsed their mouths with 20 mL of cold water to remove any residual blood, then with a plaque disclosing agent (GUM Red-Cote®, Sunstar Americas, Inc., Schaumburg, IL, USA) to aid in TPI plaque assessment.[24,25]

A subset of participants underwent a micro-sampling procedure at baseline, performed just after the OST examination. Plaque was harvested with a sterile Barnhart ½ curette from the supragingival region of one upper first molar and lower first molar where minimal restorations were present.

After baseline clinical assessments, participants underwent a dental prophylaxis checked by another study team member. An optional dental prophylaxis was offered to participants at the study end.

Treatment randomization was carried out according to a schedule provided by the Biostatistics Department of GSK Consumer Healthcare. Participants were stratified in a 1:1 ratio according to baseline number of bleeding sites (low: < 45 bleeding sites/high: ≥ 45 bleeding sites), smoking status (smoker/non-smoker) and whether they underwent bacterial sampling (yes/no). Participants were randomized to an experimental toothpaste containing 67% $NaHCO_3$ plus 1150 ppm fluoride as NaF, or a reference toothpaste containing 0% $NaHCO_3$ plus 1100 ppm fluoride as NaF (Crest® Cavity Protection; Procter & Gamble Co, Cincinnati, OH, USA; USA-marketed toothpaste). Study personnel demonstrated the amount of toothpaste to be used (approximately 1.5 g) and supervised first brushing. Thereafter, participants brushed their teeth at home twice daily for 24 weeks for one timed minute in their usual manner with their assigned toothpaste and toothbrush. The examiner, study statistician, data management staff, and sponsor employees who could influence study outcomes were blinded to treatment allocation. The blind was maintained by over-wrapping the product tubes to obscure labeling.

OST examination and MGI, BI, and TPI assessments were performed at Weeks six, 12, and 24. Subjects returned all their used assigned products at each study visit and were provided with a new diary card, toothpaste, and toothbrush (toothbrush was replaced after three months). Microbiological samples were collected at each study visit and at an additional visit at Week 32. Participants abstained from brushing or using any oral hygiene product over a 12-hour period (+5 hours, -2 hours) and from eating or drinking for at least four hours prior to each visit and until assessments were complete. They could drink water up to one hour before plaque assessments. Participants were not permitted to undergo any additional elective dental procedures or dental prophylaxis (excluding emergency dental treatment), use any oral hygiene products other than the study

products, use chewing gum, use any professional/over-the-counter whiteners or antimicrobial mouth rinses, or floss (except for removal of impacted food or if part of the participant's usual oral hygiene routine) over the course of the study.

Safety

Adverse events (AEs) and any OST examination abnormalities were recorded from the time of supervised brushing at the screening visit until five days after the last administration of study product. Clinical judgment was used to assess the relationship of any treatment-emergent AE (TEAE) to the study product.

Scoring Procedures

Gingivitis. This was assessed using the MGI[10] and the BI.[22] For the MGI, the examiner scored facial and lingual surfaces at two sites (papillae and margin) on each evaluable tooth. Each surface was scored as 0 (absence of inflammation), 1 (mild inflammation; slight color change; little texture change in any portion of, but not entire, marginal/papillary gingival unit), 2 (mild inflammation; criteria as above but involving entire marginal/papillar gingival unit), 3 (moderate inflammation; glazing, redness, edema, and/or hypertrophy of marginal/papillary gingival unit), or 4 (severe inflammation; marked redness, edema and/or hypertrophy of marginal/papillary gingival unit, spontaneous bleeding, congestion, or ulceration). MGI was calculated for each participant by adding individual scores and dividing this by total number of measurements.

For the BI,[22] the examiner engaged a World Health Organization probe with a 0.5 mm ball tip approximately 1 mm into the gingival crevice and applied a moderate pressure while sweeping from interproximal to interproximal along the sulcular epithelium. Bleeding was scored as 0 (no bleeding after 30 seconds), 1 (bleeding upon probing after 30 seconds), or 2 (immediate bleeding on probing). The BI score was calculated for each participant by adding individual bleeding scores and dividing this by the number of sites assessed. A site was considered to be bleeding if the BI score was 1 or 2.

Plaque. This was assessed using the TPI.[24,25] Plaque was disclosed using GUM Red-Cote disclosing solution and assessed by dividing each gradable tooth into six areas (mesiofacial, facial, distofacial, mesiolingual, lingual, and distolingual surfaces). Plaque was scored as 0 (no plaque), 1 (slight flecks of plaque at tooth cervical margin), 2 (thin continuous band of plaque [≤ 1 mm] at tooth cervical margin), 3 (band of plaque wider than 1 mm but covering less than one-third of tooth crown), 4 (plaque covering at least one-third, but less than two-thirds, of tooth crown), or 5 (plaque covering two-thirds or more of tooth crown). TPI score was calculated for each participant by adding individual plaque scores and dividing this by the total number of measurements. Interproximal TPI score was calculated similarly, with only mesiofacial, distofacial, mesiolingual, and distolingual surfaces.

A training exercise was not conducted for MGI and plaque assessments at the start of the study as the study had employed trained examiners who were calibrated for the indices in previous studies. Each examination day, the evaluation recorder selected two repeat participants after the first scoring was completed (without reference to the initial scores) for both the plaque and MGI assessments; the examiner completed one repeat plaque assessment and one repeat MGI assessment on each participant. Repeatability assessments were a minimum of ten minutes between initial assessments. The first and second assessments on each tooth at a given visit were cross-tabulated and a weighted Kappa coefficient (κ) was calculated, along with the 95% confidence interval (CI), to assess the intra-examiner repeatability. Repeatability was deemed Excellent, if $\kappa > 0.75$; Fair to Good, if $0.4 \leq \kappa \geq 0.75$; Poor, if $\kappa < 0.4$.

Micro-Sampling Procedure

After plaque harvesting, the curette was immersed in 4 mL sterile Calgon Ringer's solution with 10% glycerol in a sterile bijou. The two plaque samples from each participant were pooled into a single vial. Viable counts were determined from a vortexed, homogenized suspension ten-fold serially diluted in phosphate-buffered saline. Samples were plated in triplicate onto mannitol salt agar to isolate staphylococci; sabouraud dextrose agar to isolate *Candida* species; and Brilliance *Escherichia coli*/coliform selective agar (all from Thermo Fisher Scientific Inc., Waltham, MA, USA) for enumeration of *E. coli* and coliform bacteria.

Agar plates were incubated for two days at 37°C before the number of colony forming units was determined by manual plate counting. For the mannitol salt and sabouraud dextrose agar, total number of colonies were counted. For the Brilliance *E. coli*/coliform selective agar, numbers of purple (*E. coli*) and pink (coliforms) colonies were enumerated.

Statistical Analysis

Sufficient participants were screened so that a maximum of 250 (approximately 125 per treatment group) could be randomized to treatment, ensuring that approximately 114 evaluable participants per group completed the Week 24 assessment. This meant that the study would have 90% overall power to detect a mean treatment difference of four bleeding sites (approximately 20%; within-group standard deviation [SD] 8.42), with a significance level of 0.05 using a two-sided paired t-test. The estimate of SD was obtained from a previous GSK Consumer Healthcare study (data on file). The main driving force for sample size was number of bleeding sites. As both bleeding site number and MGI were required for success, a power of at least 95% was required for both variables to obtain an overall 90% power. A subset of 50 randomized participants were included in the micro-sampling assessment.

The safety population was defined as all randomized participants who received at least one dose of study treatment. The efficacy analysis was performed on the intent-to-treat (ITT) population (all participants who received study treatment and had at least one post-baseline efficacy measurement). The per protocol (PP) population was identified (those in the ITT population with at least one assessment of efficacy considered unaffected by protocol violation) but no PP analysis was performed as less than 10% of participants were excluded.

Statistical analysis of number of bleeding sites, MGI, and BI was performed using analysis of covariance (ANCOVA), including factors for treatment group, smoking status, and bacterial sampling. Baseline MGI and BI were included as covariates; baseline number of bleeding sites was not a covariate as this was accounted for within the BI covariate. TPI (overall and interproximal) was analyzed similarly, but with an additional factor for bleeding site stratification (low/high) and baseline TPI (overall/interproximal as

relevant) as a covariate. All tests were two-sided and performed at the 5% significance level. The assumption of normality and homogeneity of variance was investigated and considered satisfactory.

Bacterial counts included total aerobic count from diluted sample and *Staphylococcus* spp., *Candida* species, coliform, and *E. coli* counts from neat sample. Bacterial counts from diluted samples produced a total number less than the lower limit of detection for most participants; these were therefore considered unreliable and only counts from neat samples were considered; here counts of less than 1 were treated as 0. The sum of counts from three plates was taken as the count of a participant at a visit. At each post-baseline visit, transition rates (from non-0 to 0, from 0 to non-0) were provided for each treatment. The detection limit (DL) of the viable count assay was determined to provide additional clarity for the low numbers of bacteria being detected. At each post-baseline visit, rate of participants whose records exceeded the DL was summarized by treatment, and odds ratio between treatments was estimated using a generalized linear model (logit link) with baseline status (above DL/below DL) and treatment as factors.

Results

The first participant was enrolled in August 2014; the final participant completed in April 2015. Of the 258 participants screened, 246 were randomized to treatment and 209 completed the study (Figure 1). Two participants were withdrawn from the study due to a protocol violation (use of a prohibited medicine). Participants were aged between 18 and 70 years (mean 38.6; SD 13.5), the majority were female (61.8%) and white (86.6%). Most had < 45 bleeding sites at baseline (93.9%) and were non-smokers (89.8%; Table I). Mean baseline MGI score for all participants was 2.33 (SD 0.336), indicating moderate inflammation; mean baseline TPI score was 3.05 (SD 0.378), indicating a plaque band of at least 1 mm wide.

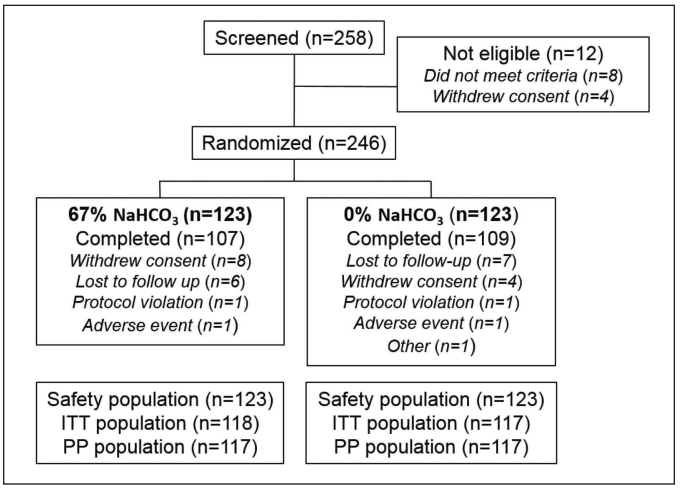

Figure 1. *Study flow.*

Table I
Baseline Demographics and Characteristics (Safety Population)

		67% $NaHCO_3$ (n = 123)	0% $NaHCO_3$ (n = 123)
Gender, n (%)	Female	74 (60.2)	78 (63.4)
	Male	49 (39.8)	45 (36.6)
Race, n (%)	White	107 (87.0)	106 (86.2)
	Black/African-American	13 (10.6)	12 (9.8)
	American Indian/Alaska native	0	1 (0.8)
	Multiple	3 (2.4)	4 (3.3)
Mean age, years (SD)		39.4 (14.28)	37.8 (12.62)
No. bleeding sites, n (%)	< 45	115 (93.5)	116 (94.3)
	≥ 45	8 (6.5)	7 (5.7)
Smoker, n (%)	No	110 (89.4)	111 (90.2)
	Yes	13 (10.6)	12 (9.8)

Efficacy

Table II shows the difference between treatments for all endpoints. Compared with the 0% $NaHCO_3$ toothpaste, the 67% $NaHCO_3$ toothpaste produced statistically significant improvements at Week 24 (primary endpoint) and at Weeks 6 and 12 (secondary endpoints), in number of bleeding sites (Figure 2) and MGI (Figure 3), all $p < 0.0001$. Statistically significant improvements in BI (Figure 4) and overall/interproximal TPI scores (Figure 5) was shown relative to the 0% $NaHCO_3$ toothpaste at all post-baseline visits (all $p < 0.0001$).

There were 74 participants in the TPI/MGI intra-examiner repeatability assessment; the Kappa score was 0.95/0.90 (both deemed Excellent), respectively.

Micro-Sampling

None of the evaluated participants (67% $NaHCO_3$ toothpaste, n=24; 0% $NaHCO_3$ toothpaste, n=36) had a staphylococcus, coliform, or *E. coli* count over the DL at any timepoint. Over time, there was an increase in yeast; however, the odds ratio comparison between groups showed no significant difference at either visit (Week 24, $p = 0.2603$; Week 32, $p = 0.2227$).

Table II
Efficacy Endpoints: Difference in Adjusted Means at Each Visit (ITT Population)

	67% $NaHCO_3$	0% $NaHCO_3$	Difference[a] (95% CI)	P-value	% Difference[b]
			Number of Bleeding Sites		
Week 6	n = 117	n = 117	-11.13 (-13.23, -9.03)	<0.0001	-47.7
Week 12	n = 111	n = 115	-8.22 (-9.97, -6.47)	< 0.0001	-34.4
Week 24	n = 109	n = 113	-11.61 (-13.19, -10.03)	< 0.0001	-46.7
			MGI		
Week 6	n = 118	n = 117	-0.44 (-0.53, -0.36)	< 0.0001	-22.6
Week 12	n = 111	n = 115	-0.42 (-0.51, -0.32)	< 0.0001	-21.8
Week 24	n = 109	n = 113	-0.65 (-0.74, -0.57)	< 0.0001	-33.9
			BI		
Week 6	n = 118	n = 117	-0.14 (-0.17, -0.11)	< 0.0001	-46.7
Week 12	n = 111	n = 115	-0.10 (-0.12, -0.07)	< 0.0001	-35.7
Week 24	n = 109	n = 113	-0.15 (-0.17, -0.12)	< 0.0001	-48.4
			Overall TPI		
Week 6	n = 118	n = 117	-0.45 (-0.55, -0.36)	< 0.0001	-15.0
Week 12	n = 111	n = 115	-0.36 (-0.45, -0.27)	< 0.0001	-12.4
Week 24	n = 109	n = 113	-0.44 (-0.53, -0.35)	< 0.0001	-15.1
			Interproximal TPI		
Week 6	n = 118	n = 117	-0.42 (-0.51, -0.34)	< 0.0001	-13.2
Week 12	n = 111	n = 115	-0.34 (-0.42, -0.27)	< 0.0001	-11.0
Week 24	n = 109	n = 113	-0.40 (-0.48, -0.32)	< 0.0001	-12.9

[a]From ANCOVA analysis; difference is 67% $NaHCO_3$ minus 0% $NaHCO_3$; a negative difference favors 67% $NaHCO_3$

[b]Percentage calculated as (difference/adjusted mean of reference)*100%

Safety

Safety is summarized in Table III. All TEAEs were mild-to-moderate in intensity and no serious TEAEs were reported. There were two participant withdrawals due to TEAEs (anterior teeth hypersensitivity and angular cheilitis in the 67% and 0% $NaHCO_3$ groups, respectively).

Table III
Treatment-Emergent Adverse Events (TEAEs) (Safety Population)

	67% $NaHCO_3$ (n = 123)		0% $NaHCO_3$ (n = 123)		Overall (n=246)	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
At least one TEAE	17 (13.8)	22	14 (11.4)	16	31 (12.6)	38
Oral TEAE	8 (6.5)	10	9 (7.3)	11	17 (6.9)	21
At least one treatment-related TEAE	1 (0.8)	2	4 (3.3)	5	5 (2.0)	7
Burning sensation	1 (0.8)	1	0	0	1 (0.4)	1
Sensitivity of teeth	1 (0.8)	1	1 (0.8)	1	2 (0.8)	2
Cheilitis	0	0	1 (0.8)	2	1 (0.4)	2
Thermal burn	0	0	1 (0.8)	1	1 (0.4)	1
Diarrhea	0	0	1 (0.8)	1	1 (0.4)	1

n (%): number (percent) of participants; nAE: number of TEAEs

Discussion

It is imperative to supplement professional dental plaque removal with appropriate oral hygiene at home to repeatedly disrupt plaque biofilm.[3-5] $NaHCO_3$-based toothpastes can reduce plaque build-up compared with those without $NaHCO_3$[12-16] and with greater efficacy than with toothpastes with other abrasive systems, such as silica or dicalcium phosphate,[12,13,15] or with bacteriostatic/bacteriocidal ingredients such as stannous fluoride, chlorhexidine, or triclosan/copolymer[13-15,26] Furthermore, a recent series of six- and 12-week studies have indicated that removal of plaque by toothpastes containing 62% or 67% $NaHCO_3$ has significant clinical benefit in terms of overall gingival health compared with non-$NaHCO_3$-containing toothpastes.[17,27]

To confirm these findings, this study was performed in participants with moderate gingivitis. However, the protocol inclusion criterion did not select a specific plaque level for acceptance. Overall, the baseline mean MGI and TPI scores were 2.33 (SD 0.330) and 3.05 (SD 0.378), which were higher than in a previous gingivitis study that had specific inclusion criteria for MGI (1.75) and TPI scores (1.50).[28] Also, a criterion for inclusion in the study was a positive response to bleeding on brushing at screening. This is confirmation that gingivitis was present at clinically significant levels. The external validity of this study is high as it was performed in a moderate gingivitis population that demonstrated significant gingival bleeding after brushing that is representative of individuals for whom the product is intended, and included an appropriate control in accordance with the US Department of Health and Human Service draft guidance for industry for the development and evaluation of drugs for treatment or prevention for gingivitis.[29] The six-month time frame was likely sufficient to allow the novelty of being part of a clinical trial to wear off, meaning that the product would be used according to each participant's usual routine.

In this study, the 67% $NaHCO_3$ toothpaste produced statistically significant improvements in measures of gingivitis and plaque compared with a 0% $NaHCO_3$ toothpaste. These differences were seen as early as six weeks and extended to six months. This study clearly demonstrates the clinically relevant long-term effect of the 67% $NaHCO_3$ toothpaste in reducing plaque build-up and recurrence of gingivitis following professional dental prophylaxis. Indeed, the mean number of bleeding sites and BI was 46–48% lower with the 67% $NaHCO_3$ toothpaste compared with the 0% $NaHCO_3$ tooth-

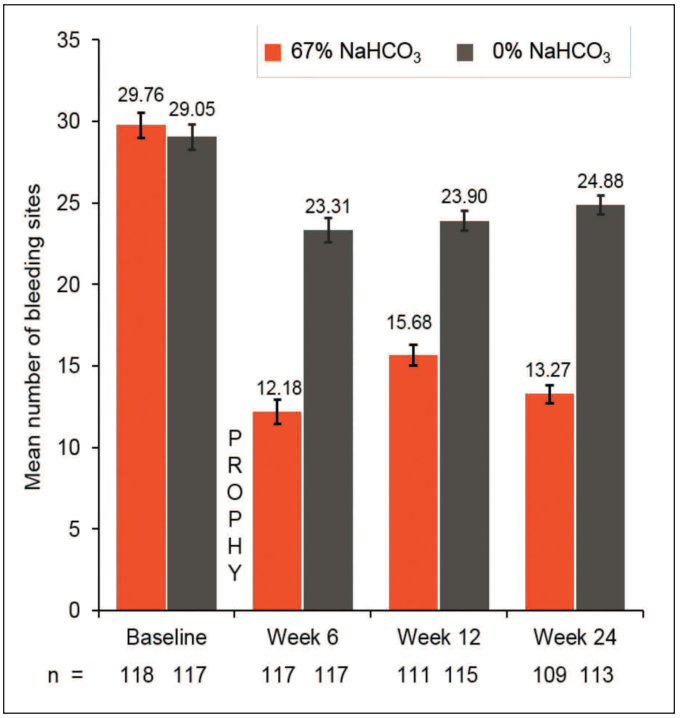

Figure 2. *Mean number of bleeding sites ± standard error,* ITT population. *Raw mean at baseline; adjusted mean at Weeks 6, 12, and 24; n = number of participants per group per timepoint.*

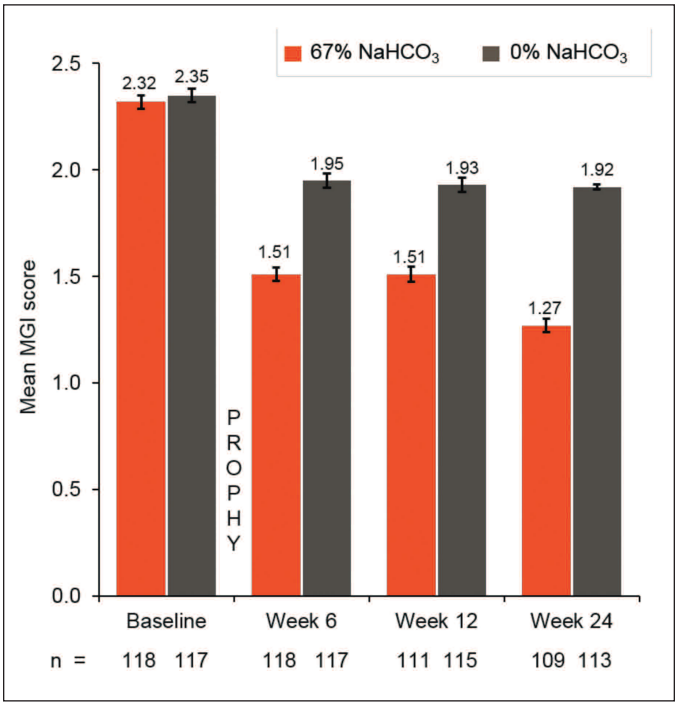

Figure 3. *Mean MGI score ± standard error*, ITT population. *Raw mean at baseline; adjusted mean at Weeks 6, 12, and 24; n = number of participants per group per timepoint. MGI was scored on a scale from 0 to 4.*

paste at Week 24. This absence of bleeding on probing is an important indicator of maintenance of periodontal health.[30] Furthermore, MGI score was a third lower with 67% $NaHCO_3$ toothpaste compared with 0% $NaHCO_3$ toothpaste at Week 24; this is particularly notable given that MGI is based on gingival inflammation, which was determined to be of moderate severity at the beginning of this study.

It has been postulated that $NaHCO_3$ exerts its efficacy through physical displacement of plaque from the tooth surface, or through making plaque more susceptible to toothbrush removal.[12,13] A recent *in vitro* study has suggested that $NaHCO_3$ disrupts the exopolysaccharide matrix structure of plaque via a non-mechanical mechanism;[7] here, plaque removal with 67% $NaHCO_3$ toothpaste was significantly better than with 0% $NaHCO_3$ toothpaste, and was also reported in the sheltered areas of the oral cavity, supporting the hypothesis that the actions of $NaHCO_3$ extend beyond mechanical disruption of plaque.

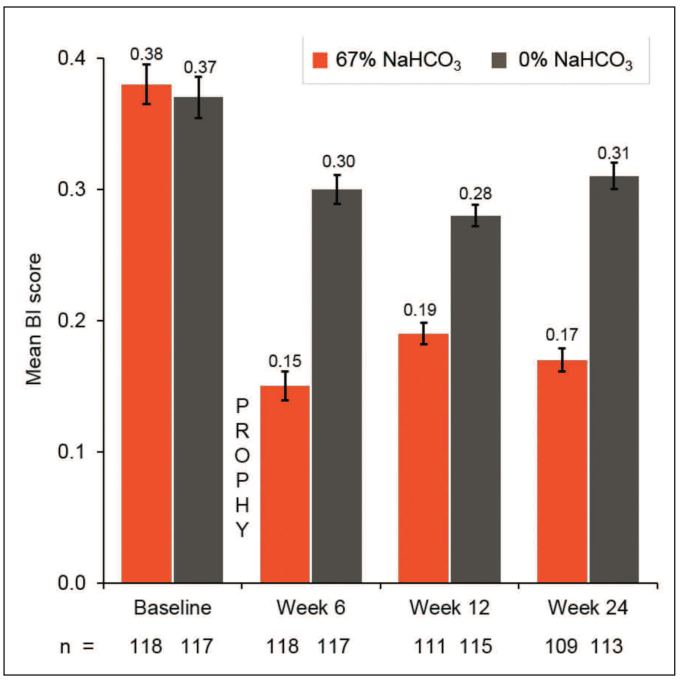

Figure 4. *Mean BI score ± standard error*, ITT population. *Raw mean at baseline; adjusted mean at Weeks 6, 12, and 24; n = number of participants per group per timepoint. BI was scored on a scale from 0 to 2.*

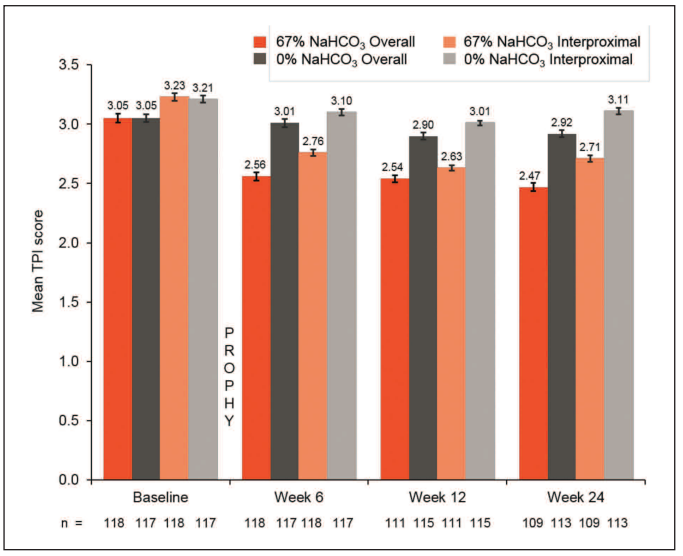

Figure 5. *Mean overall and interproximal TPI score ± standard error*, ITT population. *Raw mean at baseline; adjusted mean at Weeks 6, 12, and 24. TPI was scored on a scale from 0 to 5; Inter = Interproximal.*

In terms of tolerability, there was no evidence that the 67% $NaHCO_3$ toothpaste had an adverse effect on oral soft tissues or teeth, with only one participant experiencing AEs considered treatment related: a mild burning sensation and moderate dental hypersensitivity. Microbiological sampling found no significant difference between treatments in the proportion of participants harboring opportunistic pathogens, indicating that $NaHCO_3$ does not contribute to development of deleterious micro-organisms in the oral cavity. One limitation of the study was that blood in the toothpaste expectorate was checked only as an entry criterion; future studies could include this parameter as a measure throughout. Another limitation is that the clinical study is an examiner-blinded study (single-blind) and not a double-blinded study. The taste profile of the treatment product is very distinct due to the high concentration of the active agent (67% sodium bicarbonate) in the toothpaste. It is noted though that this study is partially limited by participants not being able to be blinded to study treatments as the regimens and sensory aspects of the treatments were different. However, while participants may have been able to discern differences, they were not informed of their study group and the toothpastes dispensed where covered with a study label that did not include any product information.

In conclusion, gingival bleeding, gingivitis, and plaque indices were significantly improved at 24 weeks with twice-daily brushing with a 67% $NaHCO_3$ toothpaste in participants with moderate gingivitis, suggesting individuals with established gingivitis may benefit from brushing with such a toothpaste. Treatments were generally well tolerated.

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Conflict of Interest: Dr. A Jose and Dr. J Pratten are employees of GSKCH; Dr. M-L Bosma was an employee of GSKCH at the time the study was performed. Dr. N Wang is an employee of ~~InVentiv~~ Health, which has received funding from GSKCH. Dr. J Milleman and Ms. K Milleman are directors of Salus Research, which has received funding from GSKCH.

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