The Procter & Gamble Company
Cincinnati, Ohio USA

Title Page

ORAL HYGIENE AND MATERNITY OUTCOMES MULTICENTER STUDY (OHMOM):

A RANDOMIZED CONTROLLED CLINICAL TRIAL TO EVALUATE LATE FIRST TO MID-SECOND TRIMESTER INTRODUCTION OF ADVANCED DAILY ORAL HYGIENE ON GINGIVITIS AND MATERNITY OUTCOMES

APRIL 8, 2013

PROTOCOL NUMBER 2011001 AMENDMENT #2

Sponsor: The Procter & Gamble Company
Worldwide Clinical Investigations—Oral
8700 Mason-Montgomery Road
Mason, OH 45040

[redacted]

PROTOCOL NUMBER 2011001

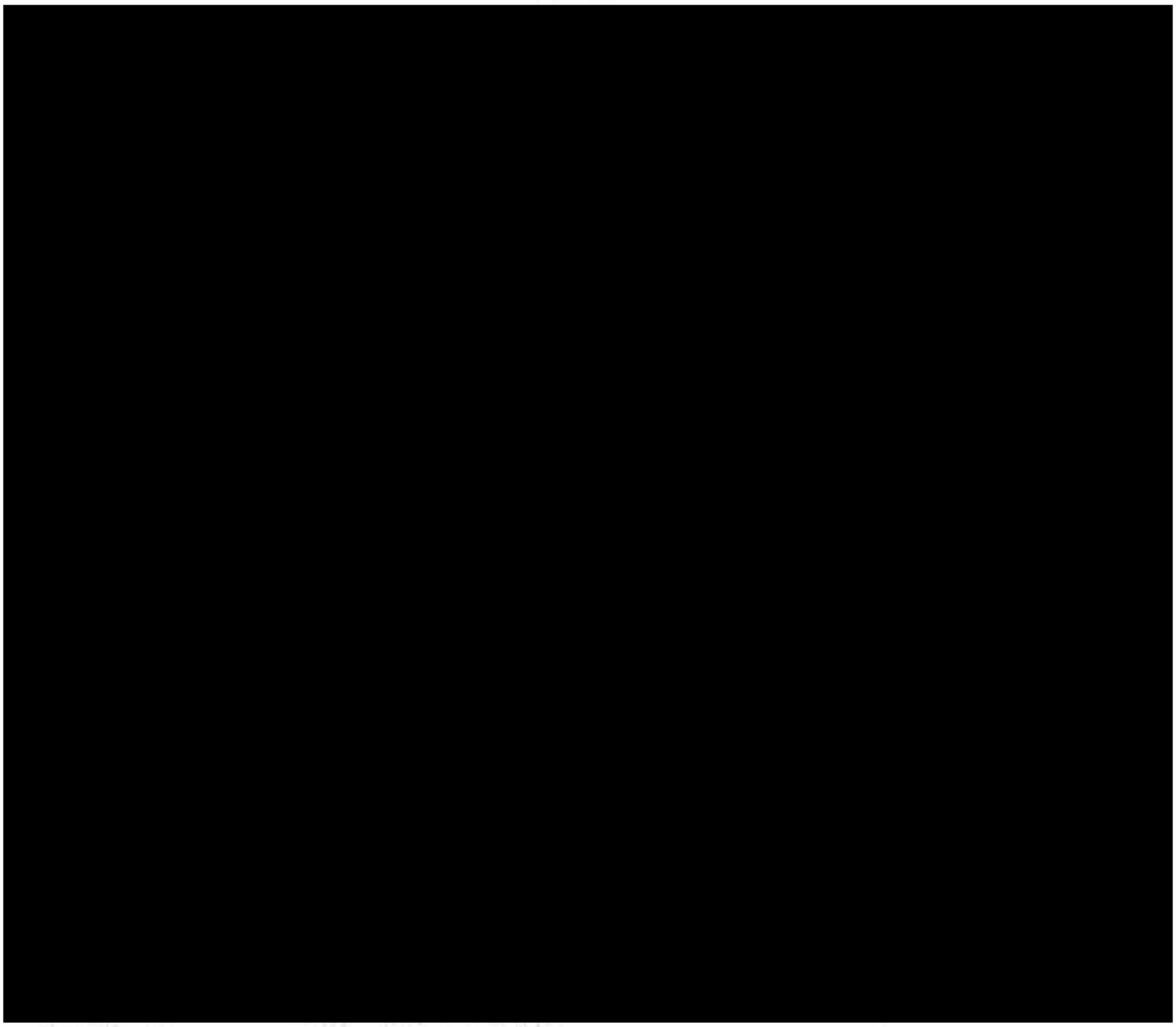

TABLE OF CONTENTS

TITLE PAGE 1

1. BACKGROUND 5
2. STUDY OBJECTIVE 6
3. OVERALL STUDY DESIGN AND PLAN 7
4. INCLUSION CRITERIA 9
5. EXCLUSION CRITERIA 9
6. CONTINUANCE CRITERIA 10
7. IDENTITY OF INVESTIGATIONAL PRODUCT(S) 10
8. PRODUCT USAGE 10
9. BLINDING, LABELING, AND SHIPPING PLAN 10
10. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS 11
11. DETERMINATION OF SAMPLE SIZE 11
12. PLANNED INTERIM ANALYSIS 12
13. SAFETY VARIABLES 12
14. EFFICACY VARIABLE(S) 13
15. INTRAORAL PHOTOGRAPHS AND SAMPLE COLLECTION 14
16. HYPOTHESES 14
17. STATISTICAL AND ANALYTICAL PLANS 15
18. DATA SAFETY MONITORING REVIEW 15
19. REFERENCES 15

APPENDIX 1: 18

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
B&A	Balance and Assignment
CFR	Code of Federal Regulations
CRF(s)	Case Report Form(s)
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCF	Gingival Crevicular Fluid
GCP	Good Clinical Practices
GI	Gingivitis Index
IRB	Institutional Review Board
LS	Löe-Silness
SOP(s)	Standard Operating Procedure(s)
TEAE(s)	Treatment-Emergent Adverse Event(s)
TMF	Trial Master File

1. Background

Gingivitis is one of the most prevalent oral diseases, affecting a majority of dentate adults.[1] Onset often begins in adolescence, and may persist throughout adulthood.[2] Marginal gingival bleeding and redness represent common clinical signs. Dental plaque plays a prominent role in the development of gingivitis, with hormonal and other factors occasionally contributing to the onset or severity of gingival inflammation.[3] Inadequate oral hygiene is recognized to contribute to plaque accumulation, and subsequent gingivitis. Gingivitis may be induced through voluntary or involuntary withdrawal of routine oral hygiene.[4] Two-to-three weeks following cessation of toothbrushing, sufficient pathogenic plaque develops to manifest clinical gingivitis in otherwise healthy individuals. Both natural and induced gingivitis can be resolved with thorough oral hygiene (brushing and flossing), or routine dental prophylaxis.

Gingivitis may be assessed through various qualitative or quantitative methods. Clinical examinations may include assessment of marginal gingival color, and/or bleeding with or without superficial provocation of gingival tissues. Some methods combine marginal color and bleeding in a single non-linear clinical index, such as the Loe-Silness Gingivitis Index (GI).[5] Assessments made be made at specific, representative sites or throughout the whole mouth.[6] Other methods may assess color, bleeding severity, location or other factors. Given the subjective nature of the clinical assessment, examiner training and calibration may play a role in gingivitis measurement.[7]

Irrespective of the method, there is considerable variation in the extent and severity of gingivitis. In one survey, gingivitis was common with US adults 18-65 exhibiting a mean of 19.4 gingival margin bleeding sites.[8] Gingivitis and bleeding scores were highest on the mandibular anterior facial and lingual sites, and maxillary posterior facial sites, bilateral symmetry was evident, and proximal sites were most commonly affected. Oral hygiene was associated with gingival inflammation and bleeding, with individuals having higher reported frequency of brushing or flossing having significantly ($p < 0.05$) lower gingivitis and bleeding. For brushing, bleeding site means were 24.2 with QD brushing, compared to 17.5 with BID brushing. For flossing, bleeding was highest (27.1 sites) with no flossing and lowest (13.1 sites) with daily flossing. Gingivitis and bleeding were also significantly ($p < 0.0001$) related to subject perceived occurrence, frequency and severity of bleeding upon brushing, and gingivitis, bleeding and plaque scores were highly correlated (0.56-0.90).

Antimicrobial dentifrices and mouth rinses are recognized to play a role in the prevention and treatment of gingivitis. Various agents have been evaluated in randomized controlled clinical trials, with or without a preceding dental prophylaxis. Chlorhexidine, essential oils combinations, triclosan, cetylpyridinium chloride and other agents have been used in dentifrice or rinse formulations.[9-12] Most of these actives target common aerobic microflora found in dental plaque. Effectiveness has been demonstrated in a few weeks or months, depending on the study model, population and others factors. Some agents, such as chlorhexidine, have been used in combination with other surgical or restorative dental care to reduce post-operative infection or inflammation.[13-15]

Some research has focused on possible relationships between gingivitis and other diseases or conditions. For example, bleeding, which has long been identified as an important objective sign of gingival inflammation, is recognized as a risk factor for progressive periodontal disease and tooth loss.[16,17] Various health conditions have been implicated in the natural history of gingivitis. Along with plaque accumulation, other conditions like pregnancy, diabetes and immune deficiency have been shown to modulate the clinical expression of gingivitis.[18] Endogenous hormones are believed to play a role in plaque-associated gingivitis seen during puberty, menstruation and pregnancy.[19] The latter, "pregnancy gingivitis", has long been recognized as archetypical with respect to the clinical characterization of gingivitis. In clinical research, pregnant women are reported to experience approximately a 20% increase in plaque and gingivitis beginning in the late first trimester, which persists or worsens during pregnancy, and returns to baseline after delivery without other interventions.[5]

While pregnancy is recognized to contribute to clinical gingivitis, studies evaluating possible relationships between periodontal disease and pregnancy outcomes have equivocal results. Early research from a case control study among 124 pregnant women in North Carolina, USA identified periodontal disease extent and severity as a significant risk factor for preterm low infant birth weight.[20] Several epidemiological and intervention studies followed, and meta-analysis of this complex research initially supported a role for periodontal treatment in reducing adverse pregnancy outcomes (birth weight or prematurity).[21] Subsequently, a few high-quality clinical trials have specifically evaluated the role of intensive periodontal intervention (usually scaling and root planing) on pregnancy outcomes. These

included two large US multicenter intervention trials with a cumulative sample size exceeding 2500 women, wherein each study failed to show an impact of periodontal therapy on pregnancy outcomes.[22,23] Meta-analysis of the updated evidence reversed earlier findings, concluding that use of scaling and root planing had no significant effect on post-natal outcomes.[24] Study design, target population and choice of intervention and others have been subsequently identified as possible contributors to the results seen in these large multicenter controlled trials.[25]

Despite its recognized prevalence in the target population, very few studies have explicitly evaluated the possible contribution of gingivitis to pregnancy outcomes.[26] Evidence continues to implicate the oral microflora in adverse pregnancy outcomes, including species associated with gingivitis. For example, in animal models, *Fusobacterium nucleatum* has been shown to induce preterm birth in the pregnant mouse, while other research has demonstrated the feasibility of the translocation of oral bacteria collected from saliva to the placenta in the mouse.[27,28] In humans, oral bacteria have been implicated in two recent adverse pregnancy outcomes, including one report of fetal demise specifically attributed to *F. nucleatum*.[29,30] Results from a recent study of women without periodontitis identified severe pregnancy-associated gingivitis on the anterior teeth due to the presence of certain oral pathogens, rather than changes in salivary hormones.[31,32]

There is long-standing evidence that onset of pregnancy gingivitis may be very low in situations with exceptional plaque control.[33] Daily oral hygiene is widely recognized as contributing to plaque control in the general adult population such as power brushes or floss, or antimicrobial-containing dentifrices or rinses to remove and/or inhibit dental plaque. Recent clinical research has shown considerable effects of combination approaches on plaque control in adults, wherein power brushes plus marketed antimicrobial dentifrices and rinses contributed to sustained reductions in overnight plaque accumulation that were comparable to levels measured immediately after a dental prophylaxis.[34,35]

Two clinical trials were conducted to assess possible effects of improved daily oral hygiene on periodontal health in pregnancy. One study in Pennsylvania, USA evaluated use of a marketed 0.07% cetylpyridinium chloride rinse during pregnancy by a high-risk population with periodontitis relative to a non-randomized control group. The test rinse was selected, in part, because it was a marketed, alcohol-free formula that had been previously shown to yield significant antiplaque and antigingivits benefits similar to an alcohol-containing positive control rinse, with high compliance, favorable user acceptability, and minor side effects similar to with cosmetic mouthrinses.[12,36] Results demonstrated that subjects using the 0.07% cetylpyridinium chloride rinse averaged a 27-site mean reduction in periodontal bleeding ($p<0.001$) during treatment, while the control group remained largely unchanged. In addition, groups differed significantly ($p<0.01$) on birth outcomes, with the rinse group exhibiting lower incidence of preterm birth under 35 weeks, along with increased gestational age and birth weight relative to the control.[37] Another study in Alabama, USA used the 0.07% cetylpyrdinium chloride rinse in combination with a 0.454% stannous fluoride dentifrice, power brush, floss and oral hygiene instruction on pregnancy gingivitis relative to a historical control. The test paste was selected, in part, because it had previously demonstrated significant ($p<0.05$) reductions in gingivitis over an 8-week period when used with a power brush with or without floss.[38] Results demonstrated that subjects using combination oral hygiene therapy had significant reductions in gingivitis and plaque, with directional reductions in preterm birth under 37 weeks relative to the control.[39] Based on the results of these two initial pregnancy studies and related studies on the effects of oral hygiene combination therapy on oral health, a multicenter randomized controlled trial was designed to evaluate use of a marketed combination oral hygiene regimen on oral health during pregnancy.

2. Study Objective

The study will evaluate the effects of introduction of an advanced daily oral hygiene program by the late second trimester of pregnancy on gingivitis in pregnant women and subsequent maternity outcomes.

3. Overall Study Design and Plan

This is a multicenter randomized, controlled, single-blind, 2-treatment, parallel group clinical trial to assess gingivitis and maternity outcomes in pregnant women who undertake an advanced daily oral hygiene program. Up to 750 subjects will be enrolled to complete the study with a target population of approximately 600 evaluable subjects. Subjects will be adult female volunteers with moderate-to-severe gingivitis who are in the late first trimester or early-to-mid second trimester of pregnancy. Sufficient screening will be conducted to enroll approximately 300 subjects at each of two study centers. After informed consent and baseline measures are recorded, qualifying subjects will be randomly assigned in equal numbers to either 1) an advanced oral hygiene regimen consisting of marketed toothbrush, toothpaste, mouth rinse and floss plus oral hygiene education counseling, or 2) regular oral hygiene with an anticavity toothpaste, regular manual toothbrush and floss. Prenatal care will remain unchanged as part of study participation, following existing medical and institutional standards for treatment. Study-related evaluations will be scheduled, where possible, as part of routine prenatal visits. Dental examinations will be conducted at Baseline before study product assignment, and monthly thereafter for 3 consecutive months of study product use. The primary outcome will be gingivitis and other clinical periodontal measures and samples will be collected. Adverse events will be collected from examination and interview. Oral hygiene and prenatal knowledge and practices will be assessed by survey at Baseline and Month 3. After Month 3, assigned oral hygiene products will be dispensed at prenatal visits or via home shipment through delivery. Maternity outcome data (gestational age) will be abstracted separately from medical records as a secondary variable, and other ancillary maternity data will be collected. An interim analysis of primary and secondary outcomes will be performed. The target population size and number of investigative sites may be adjusted as a result of the interim analysis. An independent Data Safety Monitoring Board will assess study design, conduct and outcomes at prescribed intervals using standard methods with respect to study integrity and continuance.

Table 1. Study Schedule by Procedure Type and Visit

Procedure	Baseline Visit 1	Month 1 Visit 2	Month 2 Visit 3	Month 3 Visit 4	Prenatal Visits	Maternity Outcome	Post Study
Informed Consent	X						
Medical History Review	X	X	X	X			
Concomitant Medications	X	X	X	X			
Demographics	X						
Inclusion/Exclusion Criteria	X						
Oral Hygiene Prenatal Care Survey	X			X			
Continuance Criteria		X	X	X			
Oral Examination	X	X	X	X			
Optional Intraoral Photographs	X	X	X	X			
Gingivitis Examination	X	X	X	X			
Pocket Depth Examination	X	X	X	X			
Gingival Crevicular Sample Collection	X*			X*			
Oral Bacterial Sample Collection	X*			X*			
Blood Sample Collection	X*			X*			
Product Distribution	X	X	X	X			
Oral Hygiene Instruction and Supervised Use	X						
General Comments	X	X	X	X		X	
Adverse Events	X	X	X	X		X	
Subject Accountability						X	
Maternity Data from Medical Records						X	
Optional Dental Prophylaxis							X
Complementary Package Distribution							X

*Samples will be stored and may be analyzed after primary and secondary study outcomes have been calculated. Sample analysis will be described elsewhere.

Baseline Visit 1

Subjects will be asked to read and sign duplicate copies of the informed consent form which will be witnessed by site staff. Subjects will be given one signed copy of the informed consent form and the other signed copy will be maintained as site source documentation. Personal medical history information will be reviewed and retained as site source documentation; concomitant medications, height and weight will be recorded in the study database. Demographic information and entrance criteria will be assessed. Subjects will complete a survey on oral hygiene and prenatal knowledge and practices. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Optionally, intraoral photographs may be taken. A trained and calibrated dentist will measure gingivitis and periodontal pocket depth. Gingival crevicular fluid samples and bacterial samples will be collected at two sites; sample collection sites will be recorded. Blood will be collected by venipuncture. Each sample will be stored for potential subsequent analysis. General comments and adverse events, if applicable, will be recorded.

Subjects will be randomly assigned to either the control group or the regimen group. The B&A computer program will assign a kit box number to a subject upon entry of the subject's stratification data. The subject number and kit box number will be recorded on forms provided by the Sponsor and/or suitable forms provided by the site. The kit box number assignment will be maintained and used for subsequent study product dispensing. Subjects will be given study products, instructed on product use and the first study product use will be supervised. All subjects will receive customary oral hygiene instruction, and in addition, subjects assigned to the regimen will receive counseling on oral hygiene, including an educational DVD on oral hygiene for personal use. All clinical examinations and interviews will be conducted by study personnel that are blind to treatment assignment, and uninvolved with oral hygiene education or product use training. The examiner will be in an area separate from randomization, product distribution, oral hygiene instruction and supervised use.

Month 1 Visit 2

Continuance criteria will be assessed. Personal medical history information will be reviewed and updated and maintained as site source documentation. Concomitant medications and weight will be recorded in the study database. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Optionally, intraoral photographs may be taken. A trained and calibrated dentist will measure gingivitis and periodontal pocket depth. Subjects will be given additional study products according to the kit box number assigned at the Baseline Visit. General comments and adverse events, if applicable, will be recorded.

Month 2 Visit 3

Continuance criteria will be assessed. Personal medical history information will be reviewed and updated and maintained as site source documentation. Concomitant medications and weight will be recorded in the study database. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Optionally, intraoral photographs may be taken. A trained and calibrated dentist will measure gingivitis and periodontal pocket depth. Subjects will be given additional study products according to the kit box number assigned at the Baseline Visit. General comments and adverse events, if applicable, will be recorded.

Month 3 Visit 4

Continuance criteria will be assessed. Personal medical history information will be reviewed and updated and maintained as site source documentation. Concomitant medications and weight will be recorded in the study database. Subjects will complete a survey on oral hygiene and prenatal knowledge and practices. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Optionally, intraoral photographs may be taken. A trained and calibrated dentist will measure gingivitis and periodontal pocket depth. Gingival crevicular fluid samples and bacterial samples will be collected at the same two sites sampled at Baseline; sample collection sites will be recorded. Blood will be collected by venipuncture. Each sample will be stored for subsequent analysis. General comments and adverse events, if applicable, will be recorded.

Subjects will be given an additional supply of study products according to the kit box number assigned at the Baseline Visit. Subjects assigned to the regimen will view an educational DVD on oral hygiene, and study product usage instructions will be reviewed. All clinical examinations and interviews will be conducted by study personnel that are blind to treatment assignment, and uninvolved with oral hygiene

education or product use training. The examiner will be in an area separate from product distribution, oral hygiene instruction and supervised use.

Used study products will not be returned to the clinical site; all study products are marketed oral hygiene products.

General Comments and Adverse Event Recording

General comments and AEs may be recorded at any time during the study. Any Treatment-Emergent Adverse Event (TEAE) that remains unresolved by study end should be followed up until resolution by the Principal Investigator and resolution should be documented as source documentation. If a subject is unreachable to determine whether the TEAE has been resolved, the attempts to contact the subject should be documented as source documentation.

Maternity Outcome (Record Review)

Maternity outcome data (plus ancillary variables such as birth weight) will be abstracted separately from medical records by trained personnel using standard methods. Maternal weight prior to delivery will be recorded. All maternity outcome data (including possible adverse events) will be collected from records by trained and qualified personnel who are blind to treatment assignment. A subject accountability form will be completed and subjects will be dismissed from the study. A subject accountability form will also be completed for subjects who drop out of the study prior to its completion.

Optional Post-Study Dental Prophylaxis

Subjects that have been randomized and received study products and complete the Month 3 Visit or have been dropped due to the recommendation of the Principal Investigator (i.e. have a disease or condition that in the opinion of the investigator could interfere with the safe completion of the study) will be offered a complimentary dental prophylaxis after delivery.

Post-Study Complementary Package

After completion of participation subjects that completed all study visits and had a live birth will be provided a complementary package containing marketed baby care products and replacement Oral-B® Precision Clean brush heads. In addition to the aforementioned products, subjects in the control group will receive an Oral-B® ProfessionalCare Series 1000 powered toothbrush with the Oral-B® Precision Clean brush head in the complementary package. Complementary packages will be identically sized and labeled except for a unique number used for assignment; complementary packages will be distributed according to the kit box number assigned at the Baseline Visit. Subjects that completed all study visits without a live birth will be provided a complementary gift card or equivalent compensation.

4. Inclusion Criteria

In order to be included in the study, each subject must:

- provide written informed consent prior to participation and be given a signed copy of the informed consent form;
- be at least the age of legal consent;
- be between 8 and 24 weeks of pregnancy;
- have at least 20 natural teeth;
- have moderate-to-severe gingivitis during pregnancy, including at least 30 intraoral sites with evidence of marginal gingival bleeding.

5. Exclusion Criteria

Subjects are excluded from study participation where there is:

- evidence of multiple gestations;
- history of HIV infection, AIDS, autoimmune disease, or diabetes other than gestational diabetes;
- indication for use of antibiotic pre-medication prior to dental procedures;
- systemic corticosteroid or immunosuppressive therapy within 1 month of Baseline;
- severe periodontal disease, rampant untreated dental caries, or other oral conditions that necessitate immediate dental care;
- ongoing dental care that in the opinion of the investigator could impact study participation;
- a history of allergies or hypersensitivity to mouth rinse products containing CPC;
- any disease or condition that in the opinion of the investigator could interfere with the safe completion of the study;
- randomization to a treatment in study 2011001 during a prior pregnancy.

6. Continuance Criteria

Subjects may be excluded from the study or the analysis due to:

- non-compliance with study procedures;
- use of any non-study oral hygiene products;
- antibiotic, systemic corticosteroid or immunosuppressive therapy;
- dental prophylaxis or periodontal therapy;
- any disease or condition that in the opinion of the investigator could interfere with the safe completion of the study;
- urgent dental treatment that might impact study participation;
- elective termination of pregnancy.

7. Identity of Investigational Product(s)

- Regimen: Crest® Pro-Health toothpaste (0.454% stannous fluoride), Oral-B® ProfessionalCare Series 1000 powered toothbrush with the Oral-B® Precision Clean brush head, Crest® Pro-Health Multi-Protection Mouth Rinse (0.07% Cetylpyridinium chloride) and Glide® Pro-Health Deep Clean dental floss.
- Control: Crest® Cavity Protection (0.243% sodium fluoride) toothpaste, Oral-B® Indicator regular, flat-trim, soft manual toothbrush and Oral-B® Essentials dental floss.

8. Product Usage

All subjects will be provided basic oral hygiene instruction following marketed instructions for product use. In addition, subjects assigned to the regimen group will receive oral hygiene counseling including an instructional DVD. All subjects will receive routine text message, phone, email or mail communication on upcoming visits.

Control

Subjects will be instructed to brush thoroughly twice daily. Subjects will be instructed to rinse with water after brushing. Subjects will be instructed to floss the whole mouth once daily. Subjects will be instructed to use the study products in place of usual oral hygiene for the duration of the study.

Regimen

Subjects will be instructed to apply a full brush head of toothpaste. Then, subjects will be instructed to place the brush head on the teeth and switch the brush on by pressing the on/off button. Subjects will be instructed to guide the brush head slowly from tooth to tooth, spending a few second on each tooth surface. Subjects will be instructed to brush the gums as well as the teeth, first the outsides, then the insides, finally the chewing surfaces; they should not press too hard or scrub. Subjects will brush thoroughly for 2 minutes, using the timer on the brush: a short stuttering sound at 30 second intervals is a reminder to brush equally all four quadrants of the mouth. Subjects will be instructed to rinse with water after brushing. Subjects will then rinse with 20 mL of mouth rinse for 30 seconds. Subjects will be instructed to floss the whole mouth once daily. Subjects will be instructed to brush and rinse twice daily. Subjects will be instructed to use the study products in place of usual oral hygiene for the duration of the study.

9. Blinding, Labeling, and Shipping Plan

This is a single-blind study with limited access to the randomization code. Access to the treatment codes will be managed by the Sponsor's clinical supplies organization. The treatment each subject will receive will not be disclosed to the Principal Investigator, examiners, study center personnel, subjects, contracted monitors, contracted vendors, or the Sponsor, except for select site personnel responsible for usage instruction and supervised use, and the Data Safety Monitoring Board.

The identity of the toothpastes, mouth rinse and dental floss will be disguised. The identity of the powered toothbrush will not be disguised. All control kits will contain toothpaste, a manual toothbrush, dental floss and written instructions. Regimen kits will contain toothpaste, mouth rinse, a powered toothbrush, brush head, dental floss and written instructions. Additionally, supplemental kit boxes will be provided should additional kit boxes be needed to replace a kit box. Supplemental kit boxes may be dispensed only after consulting with the Sponsor for correct supplemental kit box assignment: the subject

identification number and original kit box number must be provided to the Sponsor and the Sponsor will provide the supplemental kit box number to be dispensed.

Kit boxes will be provided with a 1 month supply of study products to be dispensed at each of the first 3 study visits and a 16-week supply will be provided to be dispensed at the fourth study visit. The regimen and control kit boxes, including supplemental kit boxes, will be identically sized; the kit box labels will be identical except for a unique kit number used for assignment. Kit boxes will be packed in a randomized fashion based on a computer-generated randomization. An encrypted randomization file used by the B&A program links kit box number and treatment assignment.

All kit box labels will contain the study number, emergency phone number, distributor name/address, appropriate caution statements, content statement and other information as required by internal regulations and clinical SOPs. Kit box content statement will be worded to maintain the study blind. The shipping containers/pallets will be labeled with the clinical site address and a content statement listing the study number and kit box numbers contained within.

The site will be provided with a code breaker report in a sealed envelope. The sealed code breaker report contains documents that list the kit box number while the identity of the treatment products is hidden by an opaque scratch-off seal. If the study blind needs to be broken, an individual subject's investigational product may be ascertained by opening the sealed code breaker report, locating the kit box number or treatment code and scratching off the opaque seal to reveal the treatment identity. The sealed code breaker report will be opened if management of the subject requires knowledge of the identity of the investigational product. The Principal Investigator should immediately inform the Sponsor that the code will be broken and record the date, time and reason for breaking the code in writing. After the study is complete and the study database has been finalized and locked, the site will return the code breaker report to the Sponsor using the self-addressed, stamped envelope provided by the Sponsor.

10. Method of Assigning Subjects to Treatment Groups

Study Design	Total n	n/site	n/group/site	Strata	Cut-offs
Parallel	750	300-450	150-300	History pre-term birth Current smoker Number of bleeding sites	Yes/No Yes/No (< 60 , ≥60)

B&A Computer Program

A separate randomization will be generated for each of the study sites with approximately equal numbers of subjects randomized at each site (300-450) and approximately equal numbers of subjects assigned to each of the treatment groups (150-300) at each study site to meet the overall recruitment target of 750 subjects. Eligible subjects will be randomly assigned equally to one of the two treatment groups. Each randomization will balance for history of pre-term birth, smoking and number of bleeding sites. Within strata, subjects will be randomly assigned to one of the treatment groups using an encoded program or randomization schedule supplied by the Sponsor.

11. Determination of Sample Size

The initial selection of sample size (n=300/group) is based on variability of gestational age from preliminary data in a similar study design without a randomized control group. The final sample size will need to be re-estimated with more accurate data from this exact design with the current study population. With a sample size of 300/group and an estimate of variability of 4.1, a difference in gestational age between the two groups of approximately 1.1 weeks with power of 90% and carrying out two-sided testing with an α=0.05 can be detected. Similarly, for the Lõe-Silness gingivitis endpoint, a difference between treatments of 0.05 using an estimate of variability of 0.185 with a power of at least 90% can be detected. To adequately size this study, an interim power calculation will be conducted after approximately 200 subjects have completed the study (approximately 100 from each study site).

Based on the interim analysis, the sample size will be adjusted by adding up to 150 subjects depending on recruitment at each site for a total of up to 750 subjects overall to i) replace non-evaluable subjects, ii) account for increased variability from the interim analyses compared to the initial estimate of variability and iii) increase power for some subset analyses.

12. Planned Interim Analysis

The interim analysis of data will be limited to sample size calculations based on the observed variability after approximately 200 subjects have completed the study (approximately 100 from each study site). The sample size of 200 is based on logistical considerations. The final determination of treatment differences will be evaluated by the statistical analysis plan with no adjustment in type I error rate since the analysis will only be for sample size estimation and no hypothesis testing or treatment difference information will be obtained. Furthermore, the treatment identity will not be revealed to the statistician carrying out the analysis or to any study or Sponsor personnel, but will be available to the DSMB.

After approximately 200 subjects have completed the study, data will be provided to a designated independent statistician that is not involved in the study or its conduct. The data provided to carry out the sample size calculations will include maternity outcomes, demographic variables and treatment code. The independent statistician will receive the treatment code via a secure transfer from the Sponsor's clinical supply organization.

The subject population to be used in the interim analysis will include only those subjects that have available maternity outcomes and demographic variables. The sample size calculations will be performed with gestational age using 80% power and 2-sided testing with the model specified in the statistical analysis plan. The delta between the treatments will be 3-5% of the control group adjusted mean (i.e., 0.05 x adjusted mean for the control group), and the error term will be estimated from the mean square error from the model specified in the statistical analysis plan.

The independent statistician will provide only the following information to the Sponsor:

- Number of subjects that contributed to the interim analysis.
- Updated sample size based on the power calculations

The outcome of the interim analysis may result in early termination of the research due to unexpected safety findings, continuing the study with the planned sample size or adjusting the sample size.

13. Medical History and Concomitant Medications

Medical history information will be recorded as source documentation. Medical history data related to prior pregnancy, smoking, drug use, height and weight will be recorded in the study database. Concomitant medication information will be recorded in the study database.

14. Safety Variables

Oral Examination

Assessment of the oral soft tissue is conducted via a visual examination of the oral cavity and perioral area utilizing a standard dental light, dental mirror, and gauze. The structures examined include the gingiva (free and attached), hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, lips, and perioral area. Assessment of the oral hard tissues will be conducted via a visual examination of the dentition and restorations utilizing a standard dental light, dental mirror, and air syringe. All abnormal findings will be recorded and categorized by their location; hard tissue findings will be categorized as "other." An Adverse Event (AE) will be recorded if a new abnormal finding is noted after product distribution or any previously noted abnormal finding increases in severity during the treatment period.

Safety Observations and/or Measurements

Safety will be assessed through clinical examinations, interviews and birth record review.

Soliciting Reported AEs

Subjects will be asked whether, since receiving study drug, they have:

- experienced any changes in well-being;
- used any new medications;
- changed medication regimens (either prescription or over-the-counter);
- been hospitalized or had any accidents.

Questions should be general in nature and should not suggest symptoms.

Medical Management of AEs

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment will be recommended. Additional follow-up will be performed as necessary and recorded as source documentation, with the results provided to the Sponsor. Subjects that experience any clinically significant AE will remain under medical supervision until the Principal Investigator recommends appropriate follow-up treatment or deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

AE Recording

When an AE occurs after written informed consent has been obtained but before the first dose of study drug, the AE will be considered a nontreatment-emergent AE. Only serious nontreatment-emergent AEs related to study procedures will be recorded in the eCRF. All nontreatment-emergent AEs that are non-serious or unrelated to study procedures should be documented by updating the medical history. An AE that occurs from the time the subject receives her first dose of study drug until her exit from the study will be considered a treatment-emergent AE (TEAE). All TEAEs will be collected. The expectedness, severity and causality of all recorded AEs will be classified.

Expectedness

Expectedness refers to a reasonable likelihood of observing an adverse event in daily life, in study procedures or with use of the study products.

Severity

Severity refers to the extent to which an AEs affects daily activities. Severity will be categorized according to the following criteria:

- Mild: Normal activities unaltered;
- Moderate: Normal activities altered;
- Severe: Unable to undertake normal activities.

The term "severity" is not the same as "serious." Seriousness, not severity, serves as the guide for defining regulatory reporting obligations (see Appendix 1).

Causality

Causality refers to the relationship of the AE to study drug. Assessment of causality is the responsibility of the Principal Investigator at each site. If this responsibility is delegated to a sub-investigator, this should be appropriately documented in the delegation sheet.

Causality will be categorized according to the following criteria:

- Doubtful: There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation.
- Possible: There is medical evidence to suggest that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.
- Probable: There is strong medical evidence to suggest that the AE is related to study drug usage.

15. Efficacy Variable(s)

Löe-Silness Gingivitis Index (GI)

The Löe-Silness GI is used to evaluate the gingiva based on color, consistency, and bleeding on probing. The entire dentition, with the exception of the third molars, is evaluated. For each tooth, six gingival areas (distobuccal, buccal, mesiobuccal, mesiolingual, lingual, and distolingual) are evaluated using adequate light, a mouth mirror, and a periodontal probe. Prior to evaluation, the teeth and gingiva are air dried as required to provide adequate visibility. The probe is inserted about 1mm into the gingival sulcus and passed from interproximal to interproximal. One aspect (either facial or lingual) of each tooth in a quadrant is first "skimmed" and then graded before passing to the next quadrant. Each of the six tooth surfaces is given a score of 0-3. A subject's full mouth GI score is determined by summing the scores and dividing by the number of sites examined. Criteria for the gingivitis scores are as follows:

Score	Criteria
0	Normal gingiva.
1	Mild inflammation – slight change in color, slight edema. No bleeding on probing.
2	Moderate inflammation – redness, edema, and glazing. Bleeding on probing.

3	Severe inflammation – marked redness, edema. Ulceration. Tendency to spontaneous bleeding.
8	Tooth not scored.
9	Tooth missing.

Due to the nature of the measurement, the Löe-Silness GI assesses both inflammation and bleeding. Gingival bleeding is derived from the GI scores at each site by assigning the site's Bleeding Score to 1 if the GI score is either a 2 or 3, and assigning it a value of 0 if the GI score is 0 or 1. The full mouth bleeding score is determined by summing the Bleeding Scores of all scored sites.

Probing Pocket Depth Measurements

Local supragingival scaling may be administered as needed to allow periodontal probing. Periodontal pocket will be measured with a periodontal probe using standard methods. For each tooth, six gingival areas (distobuccal, buccal, mesiobuccal, mesiolingual, lingual, and distolingual) are scored using adequate light, a mouth mirror, and a periodontal probe. Prior to scoring, the teeth and gingiva may be air dried as required to provide adequate visibility. The probe is inserted to the depth of the pocket, and pocket depth is measured (in mm).

Maternity Variables

For each subject, pertinent medical records are reviewed after delivery to determine maternity outcomes relating to gestational age. Neonate birth weight and Apgar score will also be recorded as ancillary variables.

16. Intraoral Photographs and Sample Collection

Intraoral Photographs

Photographs of the lips, teeth and gums only will be captured; the whole face will not be visible in the images and personally identifiable information will not accompany the photographs. Retractors may be used to hold the lips open and the teeth may be air-dried before the photograph is taken.

Gingival Crevicular Fluid (GCF) Sample Collection

Gingival crevicular fluid samples will be taken from the mesiobuccal surface of two teeth. Sampling sites will be chosen in the following order: tooth #3, tooth #14, tooth #4 and tooth #13. Sites may include mesiobuccal restorations and/or coronal restorations.

First, the quadrant test section will be isolated with cotton rolls and the tongue may be covered with gauze (if desired). Any supragingival plaque may be gently removed with a scaler. The site will be dried with a gentle stream of air; saliva should not be present at sampling site. The Periostrip paper used for the collection should only come in contact with cotton pliers to avoid cross contamination. The Periostrip will then be inserted into the pocket 1-2mm and removed after approximately 30 seconds. A Periotron may be used according to standard procedures. Samples will be collected and stored using standard methods for subsequent analysis.

Plaque Bacteria Sample Collection

A paper point will be used to collect plaque from the mesiobuccal surface of two teeth. Sampling sites will be chosen in the following order: tooth #3, tooth #14, tooth #4 and tooth #13. Sites may include mesiobuccal restorations and/or coronal restorations. Samples will be collected and stored using standard methods for subsequent analysis.

17. Hypotheses

Primary Hypothesis:

Null Hypothesis: There is no difference between treatment groups with respect to the mean Löe-Silness change from baseline score at each visit when an adjustment is made for the baseline Löe-Silness score.

Alternative Hypothesis: There is a difference between treatment groups with respect to the mean Löe-Silness change from baseline score at each visit when an adjustment is made for the baseline Löe-Silness score.

Secondary Hypothesis:

Null Hypothesis: There is no difference between treatment groups with respect to the mean gestational age when an adjustment is made for baseline demographic variables (e.g. smoking, evidence of preterm birth, etc.)

Alternative Hypothesis: There is a difference between treatment groups with respect to the mean gestational age when an adjustment is made for baseline demographic variables (e.g. smoking, evidence of preterm birth, etc.)

18. Statistical and Analytical Plans

Statistical analyses for gingivitis efficacy will be based on whole-mouth average Löe-Silness change from baseline scores (Baseline score minus post treatment score) and will be considered the primary variable. An analysis of covariance (ANCOVA) will be performed to determine treatment differences on the whole mouth average gingivitis reduction scores with the baseline gingivitis score as the covariate and also including study site as a factor. The interaction between treatment and study site will also be assessed. Additionally, 95% confidence intervals will be generated on the treatment difference for the average change from baseline scores. Separate analyses will be performed for each visit. The within-treatment difference from baseline gingivitis score will also be tested versus zero at each visit using the same ANCOVA model.

Statistical analyses to determine treatment differences for mean gestational age or other maternity endpoints will be analyzed using an analysis of variance (ANOVA) model with demographic factors such as (but not limited to) evidence of pre-term birth and smoking, and also using study site as a factor. Confidence intervals will be generated on the treatment difference of the mean gestational age.

If any of the data does not satisfy the normality criterion, analogous nonparametric methods will be employed. Additional analyses may also be performed in order to more fully understand the data. All treatment comparisons will be considered two-sided with an α=0.05 significance level. In addition, gestational age will be categorized as preterm (gestational age < 37 weeks) or term (gestational age ≥ 37 weeks) for subsequent analyses. Other categories may be used to identify very early term births. Additional subgroups may be analyzed for birth outcome data, such as subjects with deliveries greater than or equal to 20 weeks of gestational age.

Demographic and baseline variables will be summarized by treatment group, and adverse events reported or noted during the study will be documented, listed and coded by treatment group.

19. Data Safety Monitoring Review

An independent Data Safety Monitoring Board will be established for the purposes of reviewing the safety plan prior to study initiation, and safety outcomes during study conduct. The Board will be comprised of experts from the areas of dentistry, including oral surgery, oral medicine and periodontics, medicine, including obstetrics, gynecology and neonatology, and public health, including epidemiology, biostatistics and medical ethics. Activities of the DSMB will be covered in a separate charter outlining meeting schedules, responsibilities and reporting plans from open and closed sessions. At each meeting, the DSMB will be presented with analyses of safety outcomes at each meeting for assessment, including routine tabulations of adverse events, detailed documentation of serous adverse events, and any special reports, analyses or tabulations required by the DSMB.

20. References

1. Stamm JW. Epidemiology of gingivitis. J Clin Periodontol 1986;13:360-370.
2. Birnstein E. Periodontal health and disease in children and adolescents. Pediatr Clin North Am 1991;38:1183-207.
3. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121-35.
4. Loe H, Theilade E, Jensen SB. Experimental gingivitis in man. J Periodontol 1965;10:243-55.
5. Loe H. Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta Odontol Scand 1963;21:532-51.
6. Ramjford S. Devices for prevalence and incidence of periodontal disease. J Periodontol 1959;30:51-9.

7. McClanahan SF. Bartizek RD. Biesbrock AR. Identification and consequences of distinct Loe-Silness Gingival Index examiner styles for the clinical assessment of gingivitis. J Perodontol 2001;72:383-92.

8. Gerlach RW, Bartizek RD, Biesbrock AR, Dunavent JM, Gibb RD, McClanahan SF. Oral hygiene, perceived health and gingivitis occurrence, distribution and severity. J Dent Res 2006;86(Spec Iss B): Abstract 1113.

9. Grossman E, Reiter G, Sturzenberger OP, de la Rosa M, Dickinson TD, Ferretti GA, Ludlam GE, Meckel AH. Six-month study of the effects of a chlorhexidine mouthrinse on gingivitis in adults. J Periodontal Res 1986;21:33-43.

10. Lindhe J, Rosling B, Socransky SS, Volpe AR. The effect of a triclosan-containing dentifrice on established plaque and gingivitis. J Clin Periodontol 1993;20:327-34.

11. Coelho J, Kohut BE, Mankodi S, Parikh R, Wu MM. Essential oils in an antiplaque and antigingivitis dentifrice: a 6-month study. Am J Dent 2000 Sep;13(Spec No):5C-10C.

12. Witt JJ, Walters P, Bsoul S, Gibb R, Dunavent J, Putt M. Comparative clinical trial of two antigingivitis mouthrinses. Am J Dent 2005;18:15A-17A.

13. Sorensen JA, Doherty FM, Newman MG, Flemmig TF. Gingival enhancement in fixed prosthodontics. Part I: Clinical findings. J Prosthet Dent 1991;65:100-7.

14. Lambert PM, Morris HF, Ochi S. The influence of 0.12% chlorhexidine digluconate rinses on the incidence of infectious complications and implant success. J Oral Maxillofac Surg 1997;55:25-30.

15. Hermesch CB, Hilton TJ, Biesbrock AR, Baker RA, Cain-Hamlin J, McClanahan SF, Gerlach RW. Perioperative use of 0.12% chlorhexidine gluconate for the prevention of alveolar osteitis: efficacy and risk factor analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:381-7.

16. Chaves ES, Wood RC, Jones AA, Newbold DA, Manwell MA, Kornman KS. Relationship of "bleeding on probing" and "gingival index bleeding" as clinical parameters of gingival inflammation. J Clin Periodontol 1993;20:139-143.

17. Lang N, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing. A predictor for the progression of periodontal disease? J Clin Periodontol 1986;13:590-596.

18. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. J Am Dent Assoc 2006;137:1649-1657.

19. Armitrage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.

20. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R, Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodont 1996;67:1103-1113.

21. Polyzos NP, Polyzos IP, Mauri D, Tzioras S, Tsappi M, Cortinovis I, Casazza C. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a meta analysis of randomized trials. Obstet Gynecol 2009;200:225-232.

22. Offenbacher S, Beck JD, Jared HL, Mauriello SM, Mendoza LC, Cooper DJ, Stewart DD, Murtha AP, Cochran DL, Dudley DJ, Reddy MS, Geurs NC, Hauth JC. Effects of periodontal therapy on rate of preterm delivery. Obstet Gynecol 2009;114:551-559.

23. Macones GA, Parry S, Nelson DB, Strauss JF, Ludmir J, Cohen AW, Starmilio DM, Appleby D, Clothier B, Sammel MD, Jeffcoat M. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). Am J Obstet Gynecol 2010;202:14721-8.

24. Polyzos N, Polyzos IP, Zavos A, Valachis A, Mauri D, Papanikolaou EG, Tzoras S, Weber D, Messinis IE. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. Brit Med J 2010:341:c7017 doi:10.1136/bmj.c7017.

25. Han YW. Oral health and adverse pregnancy outcomes – what's next? J Dent Res 2011;90:289-293.

26. Winner G, Pihlstrom BL. A critical assessment of adverse pregnancy outcome and periodontal disease. J Clin Periodontol 2008;35:380-397.

27. Han YW, Redline RW, Li M, Yin L, Hill GB, McCormick TS. *Fusobacterium nucleatum* induces preterm and term stillbirths in pregnant mice: implication of oral bacteria for preterm birth. Infest Immun 2004;72:2272-2279.

28. Fardini Y, Chung P, Dumm R, Joshi N, Han YW. Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. Infect Immun 2010;78:1789-1796.

29. Han YW, Ikegami A, Bissada NF, Herbst M, Redline RW, Ashmead GG. Transmission of uncultivated Bereyella strain from the oral cavity to amniotic fluid in a case of preterm birth. J Clin Microbiol 2006;44:1475-1483.

30. Han YW, Fardini Y, Chen C, Iacampo KJ, Peraino VA, Shamonki JM, Redline RW. Term stillbirth caused by oral *Fusobacterium nucleatum*. Obstet Gynecol 2010:115;442-445.

31. Figuero E, Carrillo-de-Albornoz A, Herrera D, Bascones-Martinez A. Gingival changes during pregnancy: I. Influence of hormonal variations on clinical and immunological parameters. J Clin Periodontol 2010;37:220-229.

32. Carrillo-de-Albornoz A, Figuero E, Herrera D, Bascones-Martinez A. Gingival changes during pregnancy: II. Influence of hormonal variations on subgingival biofilm. J Clin Periodontol 2010;37:220-229.

33. Chaikin BS. Incidence of gingivitis in pregnancy. Quintessence Int 1977;8:81-89.

34. Gerlach RW, Biesbrock AR, Barker ML, Karpinia K, Magnusson I. Comparative clinical trial with a paste, power brush & rinse. J Dent Res 2008;87 (Spec Iss B): Abstract #1401.

35. Magnusson I, Karpinia K, Barker ML, Gerlach RW. Anti-plaque clinical evaluation of a paste, power brush, and rinse. J Dent Res 2011;90 (Spec Iss A): Abstract #1310.

36. Blenman TV, Morrison KL, Tsau GJ, Medina AL, Gerlach RW. Practice implications with a 0.07% cetylpyridinium chloride mouthrinse. Am J Dent 2005;18:29A-34A.

37. Jeffcoat M, Parry S, Gerlach RW, Doyle MJ. Use of alcohol free antimicrobial mouth rinse is associated with a decreased incidence of preterm birth in a high-risk population. Am J Obstet Gynecol 2011:205; (In Press).

38. Biesbrock AR, Bartizek RD, Gerlach RW, Terezhalmy GT. Oral hygiene regimens, plaque control, and gingival health: a two-month clinical trial with antimicrobial agents. J Clin Dent 2007;18:101-105.

39. Reddy MS, Geisinger ML, Kaur M, Bain JL, Geurs NC. Preterm birth rates in pregnant women with therapy. J Dent Res 2010;89 (Spec Iss B): Abstract #264.

APPENDIX 1:

Adverse Events

An Adverse Event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that appears or worsens in a subject during the period of observation in a clinical study. The AE may be any of the following:

- a new illness
- exacerbation of a sign or symptom of an underlying condition or of a concomitant illness
- unrelated to participation in the clinical study or an effect of the study medication or comparator drug; or
- a combination of one or more of the above factors.

No causal relationship with the study drug is implied by the use of the term "adverse event." An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. If the event fits the serious criteria, such as an extended hospitalization, it will be considered a serious AE. Conditions leading to unplanned surgical procedures may be AEs.

Immediately Reportable Adverse Event: An AE that must be reported to the Sponsor within 24 hours of the study center being informed of the AE. Immediately reportable AEs include all serious AEs (as listed below).

Serious Adverse Event: As provided by the ICH criteria, any AE that:

- results in death;
- is life threatening; (Note: The term "life threatening" refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.)
- results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject's underlying medical condition prior to entry into the study);
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect in the offspring of a subject; or
- is judged to be medically significant. (Note: A medically significant AE is a medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the outcomes listed above. Medical and scientific judgment should be exercised in deciding whether AEs appropriately meet this criterion and are immediately reportable to the Sponsor.

Advertising

Any advertisements used in recruitment of subjects must receive prior approval from the Sponsor and the IRB. A copy of the IRB-approved advertising and the documentation thereof must be provided to the Sponsor.

Data Collection

The Principal Investigator has the responsibility for ensuring that all source documents (i.e., study and/or medical records) and CRFs are completed and maintained according to the study protocol and are available at the site.

Case Report Forms

The Sponsor will supply the paper and/or electronic CRFs/data logs to be used in this study. It is the responsibility of the Principal Investigator to maintain and submit accurate and timely CRFs to the Sponsor. All hard copy CRFs/data logs will be filled out legibly in ink.

All questions should be answered. For paper CRFs, if an entry requires correction, a single line will be placed through the entry so as not to obscure the original record, the corrected entry will be initialed and dated by the individual making the change, and a reason will be given for the change. There will be no whiteouts or erasures. For electronic CRFs, if an entry requires correction, the change is made directly to the CRF in the database, the user is prompted to provide a reason for the change, and the correction is logged in by an electronic audit trail.

If, for any reason, the subject does not complete the study, an explanation will be entered on the Subject Accountability CRF. All data gathered on the subject prior to discontinuation will be made available to the Sponsor.

Source Documents

The Principal Investigator has the responsibility for ensuring that all source documents (i.e., study and/or medical records) and paper CRFs are completed and maintained according to the study protocol. Any CRF used as a source document must be identified as such in the Investigator Notebook.

Study data collected electronically will be saved on a disk or other suitable electronic media and will be left at the site at the completion of the study.

Protocol Amendments/Changes

Changes to the Protocol following Institutional Review Board (IRB) approval affecting the safety of subjects, scope/objectives of the investigation, or the scientific quality of the study will be documented as amendments. Such changes require the Sponsor, Principal Investigator, and IRB approval prior to implementation, unless immediate action is required to safeguard subject safety. Administrative/minor changes (e.g., typos, changes in the Sponsor personnel [excluding medical monitor], etc.) will be documented as revisions but do not have to be submitted as amendments unless required by the IRB. Any change in the Sponsor's monitoring staff, Clinical Trial Manager or Medical Monitor during the conduct of the study, will be reported to the Principal Investigator.

Good Clinical Practices

This study will be conducted in compliance with applicable sections of the US Federal Regulations governing informed consent (21 CFR 50), IRBs (21 CFR 56), study conduct (21 CFR 312) and the International Conference on Harmonization's Good Clinical Practice Consolidated Guidelines, [ICH-GCPs, as published by the FDA on 9 May 1997, Federal Register, Volume 62, Number 90 pages 25691-25709]). During the course of the trial, the clinical site will be monitored by the Sponsor (Clinical Trial Manager or designee) to ensure compliance with the Protocol, regulations and guidelines, adequacy of the equipment and facilities, and satisfactory data collection.

Institutional Review

Prior to study initiation, the Principal Investigator must obtain institutional review and approval of both the Protocol and the consent form, in compliance with the US Code of Federal Regulations, Title 21, Part 56 or the ICH-GCPs Consolidated Guidelines, Chapter 3. The Principal Investigator will maintain any original authorization letter(s) and forwards copies to the Sponsor. IRB approval letters should include the study title, the Sponsor's study number, the address of the IRB, date of request, and the signature of the IRB chairperson/designate. Additionally, the letter must acknowledge that both the Protocol and consent form have been approved by the IRB, with notification of any changes required. The study will not begin until the Sponsor has received written confirmation of IRB approval. This IRB shall also review the investigation at least once a year during study execution. The Principal Investigator must notify the IRB when the study concludes.

Obligation of the Principal Investigator

Following completion of the study, the Principal Investigator shall submit a final report to the Sponsor describing the conduct of the study, deviations from planned conduct, early withdrawals and subject accountability, adverse events, and other information on study conduct.

Record Retention

The Principal Investigator must retain the subject identification codes, informed consent documentation, clinical materials inventory, CRFs, medical records and other source data for a minimum of 2 years after the last regulatory approval has been received or the discontinuation of the study. The Principal Investigator must receive written authorization from the Sponsor before destroying any study document. The Principal Investigator will make records available for inspection and copying upon the request of an authorized employee of a government authority or the Sponsor. In the event the Principal Investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to another person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor.

Study Medication Dispensing, Storage and Accounting

Study products will be stored in a secure area, under environmental conditions as required by label instructions and dispensed only under the authorization of the Principal Investigator. The storage condition shall be properly

documented. Both the receipt and dispensation of all study products will be documented using forms provided by the Sponsor and additionally may be documented on suitable forms provided by the site. Study products will not be returned to the clinical site nor returned to the Sponsor following the trial.

Subject Consent

The Principal Investigator or their designee will obtain written informed consent for each subject prior to participation in the study, per the US Code of Federal Regulations, Title 21, Parts 50.25 and 50.27 and ICH-GCPs, Chapter 4, subpart 4.8. All study procedures must be explained in non-technical terms in the informed consent form.