2020089

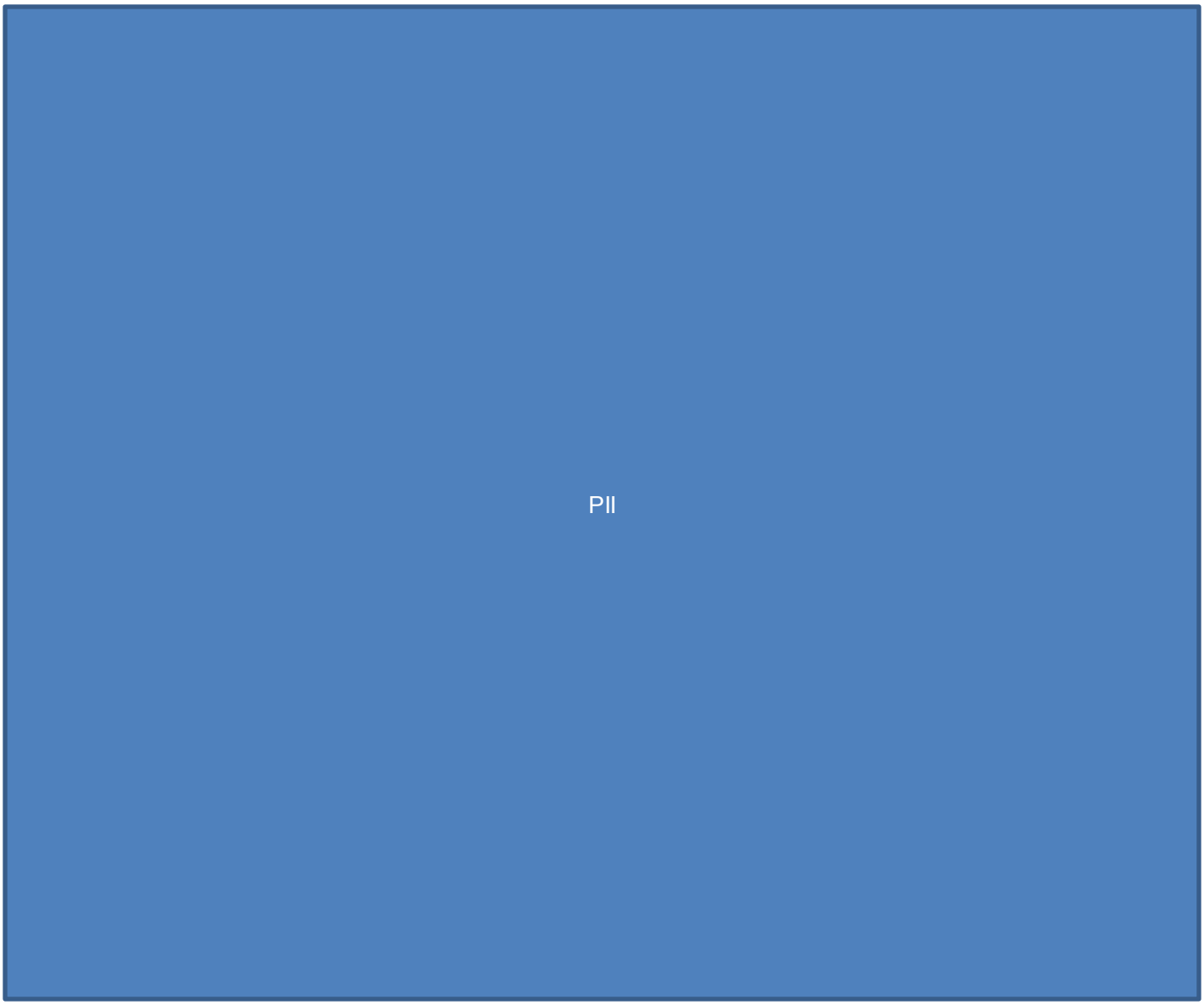
The Procter & Gamble Company
Cincinnati, Ohio USA

Title Page

A PILOT CLINICAL STUDY TO DETERMINE THE EFFECT DENTURE GEL HAS ON THE PREVENTION OF GUM ABRASIONS

12 MAY 2021

PROTOCOL NUMBER 2020089



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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADA	American Dental Association
AE	Adverse Event
CFR	Code of Federal Regulations
CRF(s)	Case Report Form(s)
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IRB/IEC	Institutional Review Board/Independent Ethics Committee
OST	Oral Soft Tissue Exam
SOP	Standard Operating Procedure

1. Study Objective

The objective of this pilot study is to evaluate the effectiveness of denture gel at treating and preventing gum abrasions while eating peanuts.

2. Overall Study Design and Plan

This is a single center, two-treatment, parallel design study. Up to 40 subjects will be enrolled with a full mandibular and full maxillary denture with a history of food related abrasions.

At each visit, an Oral Soft Tissue exam, a Mucosa Condition Assessment and a Gum Abrasion Evaluation will be performed. At Baseline, the subjects will be randomized to a treatment group. At Baseline, Week 2, and Week 4 subjects will be asked to eat 20 grams of peanuts 4 times for a total consumption of 80 g of peanuts (subjects will be permitted to take breaks if needed and drink small sips of water). Following the peanut challenge, a licensed dental professional will re-evaluate the number and size of abrasions. Subjects will receive a consumer questionnaire to complete as well prior to the Baseline, Week 2, and Week 4 assessments.

Table 1. Study Schedule by Procedure Type and Visit

PROCEDURE	BASELINE	DAYS 3, 6	WEEK 2	WEEK 4
Informed Consent	X			
Medical History Review	X			
Demographics	X			
Inclusion/Exclusion Criteria	X			
Randomization	X			
Continuance Criteria		X	X	X
OST	X	X	X	X
Mucosa Condition Assessment	X	X	X	X
Pre-Peanut Gum Abrasion Evaluation	X	X	X	X
Product distribution/instruction	X			
Subject eats 80 g of peanuts (20g, 4 times)	X		X	X
Post-Peanut Gum Abrasion Evaluation	X		X	X
Questionnaire*			X	X
General Comments	X	X	X	X
AEs	X	X	X	X
Subject Accountability				X**

*This questionnaire will be analyzed outside of this protocol.

**Subject accountability will be completed after subjects complete the study at any time.

Baseline

Prior to the Baseline, subjects will be asked to refrain from eating approximately 4 hours prior to their appointment. Previously screened subjects will review and sign an informed consent and receive a copy at the Baseline visit. The subjects' medical history will be collected or updated on site source documents. Demographic information and Inclusion/Exclusion Criteria will be obtained and documented on the appropriate case report form (CRF).

Subjects will be asked to remove their mandibular and maxillary full dentures and the dentures will be cleaned (if applicable) and examined by a dental professional. An OST will be performed followed by a Mucosa Condition Assessment, and a baseline pre-peanut challenge Gum Abrasion Evaluation.

Subjects will be asked to eat 20 grams of peanuts 4 times for a total consumption of 80 g of peanuts (subjects will be permitted to take breaks if needed and drink small sips of water). Additionally, subjects will be timed for each peanut challenge. If subjects are unable to finish the peanuts due to being too full or for any other reason, this will be noted in the eCRF General Comments. After completion of the peanut challenge, subjects will have a post-peanut challenge Gum Abrasion Evaluation.

Next subjects will be randomized to one of two treatments balanced on their baseline post-peanut challenge gum abrasion evaluations (area and number) mucosa condition, and age. The subjects will receive their products and site staff will review and provide written product use instructions.

Subjects will be reminded to refrain from eating approximately 4 hours prior to next visit.

Day 3, 6

Continuance criteria will be assessed. Subjects will be asked to remove their mandibular and maxillary full dentures and the dentures and subjects' mouths will be cleaned by a dental professional if applicable. An OST will be performed followed by a Mucosa Condition Assessment and then a Gum Abrasion Evaluation. Subjects will be reminded to refrain from eating approximately 4 hours prior to next visit.

Week 2

Continuance criteria will be assessed, and subjects will be asked to complete a questionnaire. Subjects will be asked to remove their mandibular and maxillary full dentures and the dentures and subjects' mouths will be cleaned by a dental professional if applicable. An OST will be performed followed by a Mucosa Condition Assessment and then a pre-peanut challenge Gum Abrasion Evaluation.

Subjects will then be asked to eat 20 grams of peanuts 4 times for a total consumption of 80 g of peanuts (subjects will be permitted to take breaks if needed and drink small sips of water). Additionally, subjects will be timed for each peanut challenge. If subjects are unable to finish the peanuts due to being too full or for any other reason, this will be noted in the eCRF General Comments. After completion of the peanut challenge, subjects will have a post-peanut challenge Gum Abrasion Evaluation. Subjects will be reminded to refrain from eating approximately 4 hours prior to next visit.

Week 4:

Continuance criteria will be assessed, and subjects will be asked to complete a questionnaire. Subjects will be asked to remove their mandibular and maxillary full dentures and the dentures and subjects' mouths will be cleaned by a dental professional if applicable. An OST will be performed followed by a Mucosa Condition Assessment and then a pre-peanut challenge Gum Abrasion Evaluation.

Subjects will then be asked to eat 20 grams of peanuts 4 times for a total consumption of 80 g of peanuts (subjects will be permitted to take breaks if needed and drink small sips of water). Additionally, subjects will be timed for each peanut challenge. If subjects are unable to finish the peanuts due to being too full or for any other reason, this will be noted in the eCRF General Comments. After completion of the peanut challenge, subjects will have a post-peanut challenge Gum Abrasion Evaluation. Subjects will return their kit boxes and will be dismissed from the study.

General Comments and Adverse Events, if applicable, will be recorded. Subject Accountability will be recorded as subjects are dismissed from the study at any point.

3. Inclusion Criteria

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

1. Be 18 years of age;
2. Read, sign, and receive a copy of the Informed Consent prior to initiation of study procedures;
3. Have a full maxillary and mandibular denture and wear on a daily basis;
4. Have a history of food particles getting under their full denture and causing gum irritation;
5. Are willing to abstain from eating at least four hours prior to the visits;
6. Are willing to eat 4 X 20 grams of peanuts three times (Baseline, Week 2 and Week 4) without denture adhesive;
7. Clean their dentures on a daily basis;
8. Agree not to change their regular denture cleaning routine;
9. Agree to abstain from using denture adhesive during the study;
10. Agree to not participate in any other oral/dental product studies during the study.

4. Exclusion Criteria

Subjects are excluded from study participation if they:

1. Exhibit evidence of obvious oral pathology, as determined by the Study Dentist, as a result of a mandatory OST examination on the first day of the study;
2. Are allergic to any of the ingredients contained in the study product gel;
3. Are allergic to peanuts;
4. Wear dentures overnight;
5. Are insulin-dependent and/or have any health condition(s) which would prevent compliance with study procedures;
6. Are routinely using denture adhesive;
7. Present with any disease or conditions that could be expected to increase their susceptibility to gum abrasion (like diabetes or xerostomia); or
8. Present with any disease or conditions that could be expected to interfere with examination procedures or the subject's safe completion of the study.

5. Continuance Criteria

Subjects may be excluded from the study or the analysis if they:

1. Become intolerant to study procedures;
2. Develop insulin dependence and/or any health condition(s) which would prevent compliance with study procedures;
3. Did not abstain from eating at least four hours prior to the visits;
4. Have their denture altered during study;
5. Use denture adhesive;
6. Change their denture cleaning routine;
7. Wear their denture overnight;
8. Develop any disease or conditions that could be expected to increase their susceptibility to gum abrasion (like diabetes or xerostomia); or
9. Are non-compliant with the protocol.

6. Identity of Investigational Product(s)

- **Control**: Current Denture Care
- **Treatment**: Current Denture Care + Treatment Gel

7. Product Usage

<u>Control Group:</u>
Evening denture care:

In the evening subjects will perform their regular denture cleaning routine (if subjects brush their oral mucosa with brush, they will be allowed to continue doing so). They will be instructed to sleep without dentures.

Treatment Group:
Evening denture care:
In the evening subjects will perform their regular denture cleaning routine. They will be instructed to sleep without dentures.

Evening gel application:
Subjects will rinse out their mouth with water (if subjects brush their oral mucosa with brush, they will be allowed to continue doing so) and apply gel to their mucosa where they normally wear upper or lower denture.

Subjects will apply gel in the following order, reapplying gel onto the applicator each time:

- onto the mucosa (right half) under the upper denture
- onto the mucosa (left half) under the upper denture
- onto the mucosa (right half) under the lower denture
- onto the mucosa (left half) under the lower denture

Subjects will leave the gel overnight.
Subjects will not eat or drink anything in the evening after applying the gel.

8. Blinding, Labeling, and Shipping Plan

The take home kit boxes for the Control Group will contain a subject instruction sheet. The take home kit boxes for the Treatment Group will contain disguised and labeled gel, an applicator, and a subject instruction sheet. All instructions will be given (written and verbal). All labels will contain the study number, emergency phone number, distributor name/address, appropriate caution statements, and other information as required by internal regulations and clinical Standard Operating Procedures (SOPs). The shipping containers will be labeled with the "ship to" clinical site address and a "content statement" listing study number and number of kit boxes contained within. Supplemental product will be provided to the site.

9. Method of Assigning Subjects to Treatment Groups

Subjects who meet enrollment criteria will be stratified based on Baseline post-challenge number of lesions (< 1.6 vs. ≥1.6), size of lesion (<16mm vs ≥16mm), mucosa condition (≦ 1 vs. ≥ 1), and age (≦ 64 vs. >64).

Subjects will then be randomized to one of the two (2) treatment groups using a balance and assignment procedure on site. This assignment process and the distribution of test products will be conducted in a protected area that will ensure blinding of the examiner to the identity of the test products. Product will be distributed according to a randomization schedule provided by the Sponsor. Product distribution and product return will be recorded on the Clinical Materials Inventory provided by the Sponsor. Subjects from the same household will be assigned to the same treatment group. The balance and assignment cut points may be adjusted during the study.

10. Determination of Sample Size

The sample size of 40 subjects was chosen for logistical reasons.

11. Safety Variables

Safety Observations and/or Measurements
Safety will be assessed by the absence of irreversible side effects.

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 ridge , hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, lips, and perioral area. All abnormal findings will be recorded and categorized by their location. An 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. Subjects who experience an AE may be examined by the Medical Monitor, if necessary.

12. Efficacy Variable

Gum Abrasion Evaluation:

A dental professional will assess the gingiva for any gum abrasions. A periodontal probe will be used to measure the size of any presenting abrasions and will be documented in the eCRF. The gum abrasion will continue to be measured throughout the duration of the study to track healing of the abrasion.

Staining Procedure

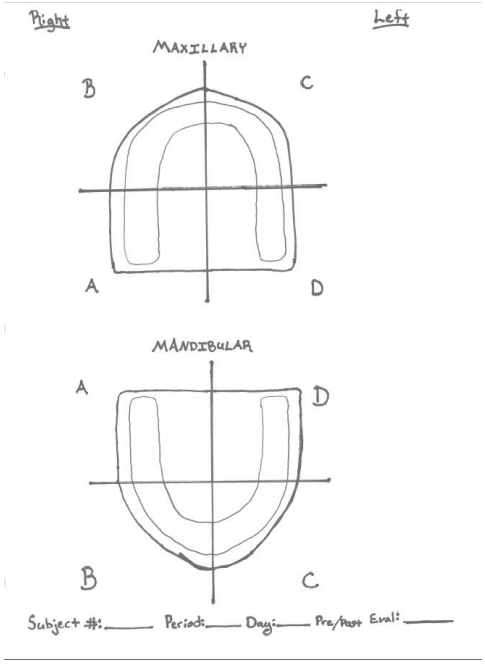
Staining solution: Mira-2-Ton (Mira-2-Ton® Hager & Werken GmbH & Co. KG. Duisburg, Germany) – same batch of stain solution will be used through the whole study.

Prior to the staining oral mucosa will be dried with the air blast. Subjects will swish 5 mL of Mira-2-Ton dye for 10 seconds followed by 5 mL of water for 10 seconds as well.

Abrasion assessment

Prior to the assessment, the mucosa under the denture will be dried with the air blast. During the measurement, the size of each lesion (colored dark blue) will be measured using periodontal probe (assessing the length and width of the lesion). The location of the lesion(s) will also be documented on the diagram below, including whether the lesion is on the ridge or the mucosa (Pre-challenge Abrasion Evaluation). The assessment notes on Figure 1 below will be summarized into ECRF. All abrasion assessments will be carried out in the same quadrant ordering. Loosely attached discolorations will be excluded from evaluation. If examiner has difficulty with assessment (plaque or abrasion), she/he will carefully try to remove the staining (non-removable stains will be assessed as abrasion). After the peanut eating exercise (no adhesive period), subjects will be instructed to rinse out their mouth till all of the particles are removed and the oral mucosa under the denture will be re-stained again prior to the 2nd assessment (Post-challenge Abrasion Evaluation).

Figure 1. The location (and shape) of each gingival abrasion would be drawn on a maxillary and mandibular denture ridge chart.



The exact dimension (as measured with the periodontal probe) of the abrasion will be recorded. For analysis purposes, abrasion might be divided into the following categories:

- small, if Ø ≤ 2.5 mm,
- medium, if Ø > 2.5, but ≤ 5 mm,
- large, if Ø > 5 mm.

Images (traditional or 3D) of abrasions might be taken for documentation and exploratory purposes.

Mucosa Condition Assessment:

The entire mucosal region under the denture will be assessed with one score per arch.

0 = pink firm tissue absent of redness and inflammation; 1 = mild redness or inflammation – slight change in color and little change in texture; 2 = moderate redness and/or inflammation – moderate glazing, redness, edema and hypertrophy 3 = severe redness and/or inflammation – marked redness and hypertrophy

13. Hypotheses

Treatment

Null Hypothesis: There is no difference between treatment groups for the abrasion endpoints (number of abrasions and size of abrasions, and mucosa assessment) across first 7 days after adjusting for the respective Baseline visit post-challenge abrasion endpoint.

Alternative Hypothesis: There is a difference between treatment groups in abrasion endpoints (number of abrasions and size of abrasions, and mucosa assessment) across first 7 days after adjusting for the respective Baseline visit post-challenge abrasion endpoint.

Prevention

Null Hypothesis: There is no difference between treatment groups for the abrasion endpoints (number of abrasions and size of abrasions, and mucosa assessment) across weeks 2 and 4 after adjusting for the respective Baseline visit post-challenge abrasion endpoint.

Alternative Hypothesis: There is a difference between treatment groups in abrasion endpoints (number of abrasions and size of abrasions, and mucosa assessment) across weeks 2 and 4 after adjusting for the respective Baseline visit post-challenge abrasion endpoint.

14. Statistical and Analytical Plans

To assess the impact of the product on the treatment of lesions, the average size of the Pre-challenge Abrasions (in mm) and the average Number of Pre-challenge Abrasions, and Mucosa Assessment across days 3 and 6 will be analyzed using a repeated measures analysis of covariance with factors in the analysis for treatment, day and respective baseline post-challenge lesion variable as the covariate. The treatment by baseline lesion and treatment by day interactions will be assessed at the 10% level. Additionally, the by day responses will also be carried out separately from the repeated measures model,

To assess the impact of the product on the prevention of lesions, the average size of the Pre-challenge Abrasions (in mm), the average Number of Pre-challenge Abrasions, and Mucosa Assessment across weeks 2 and 4 will be analyzed using a repeated measures analysis of covariance with factors in the analysis for treatment, week and respective baseline post-challenge lesion variable as the covariate. The treatment by baseline lesion and treatment by week interactions will be assessed at the 10% level. Additionally, the by week responses will also be carried out separately from the repeated measures model,

The size of the Pre-challenge Abrasions might be collapsed into pre-defined categories.

Additional analysis of the data might be carried out for exploratory purposes. If the data does not satisfy the normality assumption, then a non-parametric analysis will be utilized. All statistical tests will be two-sided with 10% Type I error rate.

Demographic data will be summarized for all subjects randomized in the study.

APPENDIX

Adverse Event Reporting

Abnormal findings which may qualify as AEs are those that: 1) were not present at Baseline and occurred after product usages of any duration, or, 2) were present at Baseline and worsened in severity after product usage of any duration. All AEs will be recorded on the CRF. If a question should arise about the causal relationship of an AE to product usage, the Medical Monitor will be contacted to make the determination of relatedness.

An ***unexpected*** event is defined as one that is not identified in nature, severity, or frequency in the current safety assessment. The events will be reported to the FDA as required, upon receipt of pertinent clinical data and completion of the required forms.

Any clinically significant abnormal laboratory finding, serious or unexpected AE, or medical event which results in the withdrawal of a subject from the study, must be followed to resolution with appropriate medical management, or as deemed necessary (with the Sponsor's agreement).

Advertising

Any advertisements used in recruitment of subjects must receive prior approval from P&G and the Investigator's IRB. A copy of the IRB-approved advertising and the documentation thereof must be provided to P&G.

Data Collection

The 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.

Any biological samples collected from subjects will be stored by the P&G lab. After a time period of two years from the last study visit, any remaining samples will be discarded. The P&G lab will provide a statement of proof to the sponsor's Clinical Trial Manager.

Case Report Forms

The Data Manager will supply the paper and/or electronic CRFs to be used in this study. It is the responsibility of the Investigator to maintain and submit accurate and timely CRFs to the Sponsor. All hard copy CRFs 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.

As necessary, the Data Manager may make specified allowable changes to the database without issuing a query to the site, as agreed upon by study site per this protocol. Examples of allowable changes include incorrect date formats, incorrect current year recorded (as in the start of a new year), and unambiguous spelling errors. Changes to common abbreviations and symbols to equivalent text to meet system or coding constraints (e.g., @ = at, ~ = approximately), may also be allowable. Values that are ambiguous or open to interpretation will be queried to the sites. It is the responsibility of the Data Manager to ensure all changes are supported by information contained elsewhere and/or are unambiguous.

Source Documents

The 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. Any CRF used as a source document must be identified as such in the Investigator Notebook.

Protocol Amendments/Changes

Changes to the Protocol following IRB approval affecting the safety of subjects, scope or objectives of the investigation, or the scientific quality of the study will be documented as amendments. Such changes will require the Sponsor, Investigator, and IRB approval prior to implementation, unless immediate action is required to safeguard subject safety. Administrative or minor changes (e.g., typographical errors, changes in Sponsor personnel, etc.) will be documented as revisions but may not need 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 Investigator.

Good Clinical Practices

This study is classified non-AMG, non-MPG according to German study classification but conducted in compliance with applicable sections of the US Federal Regulations governing informed consent (21 CFR 50) and IRBs (21 CFR 56). The conduct of this study will be in accordance with ICH-GCPs as published by the FDA, with the Commission Directive 2005/28/EC published by the European Union, and ISO 14155:2011. During the course of the trial, the clinical site will allow monitoring by the Sponsor (Clinical Trial Manager or designee) to check compliance with the Protocol, regulations and guidelines, adequacy of the equipment and facilities, and satisfactory data collection.

Institutional Review

Prior to study initiation, the Investigator must obtain institutional review and approval of the Protocol, the consent form, and other necessary study-related documents in compliance with the US Code of Federal Regulations, Title 21, Part 56 or the ICH-GCPs Consolidated Guidelines, Chapter 3 and in compliance with Procter & Gamble SOP QS-CL-05 ("Institutional Review Board/Independent Ethics Committee Review and Approval"). The Investigator will maintain any original authorization letter(s) and will be available for review by the Sponsor. IRB approval letters should include the study title, Sponsor study number, the address of the IRB, date of request, and the signature of the IRB chairperson or designate. Additionally, the letter must acknowledge that both the Protocol and consent form have been approved by the IRB. The study will not begin until the Sponsor has received confirmation of IRB approval. The IRB shall also review the investigation at least once a year during study execution. The Investigator will notify the IRB when the study is terminated and provide confirmation that the study has been closed with the IRB to the Sponsor.

Investigator Final Report

Following completion of the study, the 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. The Investigator's IRB may require more frequent status reports.

Records Retention

The Investigator must retain the subject identification codes, informed consent documentation, clinical materials inventory, CRFs (paper or electronic media), 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 Investigator must receive written authorization from the Sponsor before destroying any study document. The Investigator will make the records available for inspection and copying upon the request

of an authorized employee of a government authority or the Sponsor, at reasonable times. In the event the 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.

The Research Participant's identification codes are a unique identifier assigned by the Principal Investigator to each trial subject to protect the Research Participant's identity and privacy. The identification codes are used in lieu of the Research Participant's name when the Principal Investigator reports all adverse events and other trial related data. These codes will be used on all study documents for the Research Participant's confidentiality, in order to protect the confidentiality of information concerning Research Participants, as stated in section 2.11 of the International Conference on Harmonization Good Clinical Practice: Consolidated Guideline (ICH-GCP).

Serious Adverse Event Reporting

A *serious adverse event* is defined as an event, which suggests a definite hazard or handicap to the subjects. Serious adverse events are any events resulting in death, life threatening situation, disability or permanent damage, hospitalization or prolongation of existing hospitalization, or congenital anomaly/birth defects; events requiring intervention to prevent permanent impairment/damage; or other serious (important) medical events.

When an Investigator is notified of a serious AE, the Investigator must promptly (within 24 hours) notify the Sponsor (Clinical Trial Manager or the Medical Monitor) of the serious or unexpected event, regardless of causality. Within 5 working days, a written and/or electronic report describing the circumstances of the event must be submitted to the Sponsor. The Investigator will be responsible for SAE reporting to the IRB.

Study Medication Dispensing and Storage

Study products will be stored in a secure area, under environmental condition as required by label instructions or as described in the Protocol and dispensed only under the authorization of the Investigator. The storage condition shall be properly documented. Both the receipt and dispensation of all test products (used and unused) will be documented using forms provided by the Sponsor or suitable forms provided by the site. Study products will be returned to the Sponsor following the trial, or alternatively, they will be destroyed at the clinical site provided the site has an existing SOP for the destruction of clinical materials and prior written approval from the Sponsor.

Subject Consent

The Investigator 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 and in compliance with Procter & Gamble SOP QS-CL-04 ("Informed Consent Form, Ethics Approval and Investigator Use"). Subjects, or their legal guardian, are required to read, sign and date an IRB approved consent form with the Investigator also maintaining a signed and dated copy. The subject or legal guardian will be given a copy of the consent form. All study procedures must be explained in non-technical terms.