The Procter & Gamble Company
Cincinnati, Ohio USA

A CLINICAL STUDY TO EVALUATE DRY MOUTH RELIEF AFTER USING AN EXPERIMENTAL MOUTH RINSE COMPARED TO A WATER CONTROL

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Signatures below indicate approval of the Protocol.

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

[redacted]

PII

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)
B&A	Balance and Assignment
CDA	Confidentiality Disclosure Agreement
CFR	Code of Federal Regulations
CRF(s)	Case Report Form(s)
DMI	Dry Mouth Inventory Questionnaire
ECRF	Electronic Case Report Form(s)
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IRB/IEC	Institutional Review Board/Independent Ethics Committee
MD	Moisturization and Dryness Questionnaire
PPAQ I	Product Performance and Attributes Questionnaire I
PPAQ II	Product Performance and Attributes Questionnaire II
SOP(s)	Standard Operating Procedure(s)

PROTOCOL BODY

1. Background

Xerostomia or dry mouth is a subjective sensation of oral dryness. It affects 5.5 to 46% of the adult population with higher prevalence in females and older people (however this condition is not related to age itself). The degree of xerostomia and salivary hypofunction do not always correlate with each other. Xerostomia may be caused by a variety of underlying etiologies, including systemic diseases (diabetes, cardiac disease, cancer and cancer treatments, rheumatoid arthritis, Alzheimer's disease, Parkinson's disease, HIV/AIDS, Sjögren's Syndrome, anemia), medications, head and neck radiation and modifiable lifestyle factors (smoking, sleep apnea, alcohol use etc.). Treatment of clinical symptoms of xerostomia can be divided into two categories: systemic sialagogues (pilocarpine and cevimeline) and topic agents like saliva substitutes, topical lubrication products, candies, chewing gum and water.

Ref: Etiology, evaluation, and management of xerostomia Jillian W. Millsop, Elizabeth A. Wang, Nasim Fazel. Clinics in Dermatology. Volume 35, Issue 5, September–October 2017, Pages 468-476

2. Study Objective

The objective of this study is to evaluate dry mouth relief in subjects with self-reported feeling of dry mouth after using an experimental mouth rinse or a positive control compared to a water control.

3. Overall Study Design and Plan

This is a randomized, 3-treatment, parallel study for subjects with self-reported dry mouth symptoms as determined by an Oral Examination and subject responses to the Dry Mouth Inventory (DMI) questionnaire (see section 12) at the Acclimation visit. Qualified subjects will be randomly assigned to one of three treatments at the Baseline visit. Safety will be assessed by Oral Examinations at Baseline/Day1 and Day 8. Subjects will complete questionnaires before product use, immediately after product use, and after 30 minutes, 1 hour, 2 hours, 4 hours and 6 hours of product use on Baseline/Day 1 and Day 8. The PPAQ II questionnaire will be completed on the morning of Day 8 (see study schedule for details).

Table 1. Study Schedule by Procedure Type and Visit

Procedures	Acclimation Visit 1	Baseline/ Day 1 Visit 2	Day 8 Visit 3
Informed Consent	X		
CDA	X		
Medical History	X		
Demographics	X		
DMI Questionnaire	X		
Inclusion/Exclusion	X		
Acclimation Product Distribution	X		
Continuance Criteria		X	X
Baseline MD Questionnaire		X	
Oral Examination	X	X	X
Treatment Randomization		X	
Treatment Product Distribution		X	
Product Use		X	X
Immediate MD Questionnaire		X	
PPAQ I/ MD Questionnaire- 30 minutes		X	X**

PPAQ I/ MD Questionnaire- 1 hour		X	X**
PPAQ I/ MD Questionnaire- 2 hour		X	X**
PPAQ I/ MD Questionnaire- 4 hour		X	X**
PPAQ I/ MD Questionnaire- 6 hour		X	X**
PPAQ II Questionnaire			X*
Product Diary Distribution		X	
Product Diary Return			X
Treatment Product Return			X
General Comments	X	X	X
AEs		X	X
Subject Accountability			X

* PPAQ II will be completed at home immediately after waking up. ** No MD Questionnaire will be asked on Day 8

All questionnaires (except for PPAQ II) will be conducted over the phone by site staff. Subjects will have paper copies of the questionnaires as a reference. Site staff will directly enter the subject responses into the study database. Before asking the questions, site staff will ensure that all study procedures were followed (i.e. no eating or drinking). Product diaries will be completed on paper and reviewed outside the study database.

Acclimation (Visit 1)

At the site, subjects will be asked to read and sign an informed consent form and Confidentiality Disclosure Agreement (CDA) and will receive a signed copy for their records. Personal medical history information will be reviewed and retained as site source documentation. Demographic information will be recorded, and subjects will answer the DMI questionnaire to ensure study eligibility. An Oral Examination will be performed. Entrance criteria will be assessed. Up to 150 qualifying subjects will receive acclimation toothbrush, toothpaste, and usage instructions. Subjects will begin using these acclimation products in place of their normal oral hygiene products for the duration of the study. They will be instructed to brush their teeth in the morning of Baseline/Day 1 and Day 8 study visits.

Baseline/Day 1 (Visit 2)

Continuance criteria will be assessed. Subjects will have an Oral Examination at the site. Subjects will be randomly assigned to one of three treatment groups by a Balance & Assignment (B&A) program based on age and DMI severity score. Assigned treatment product kit boxes will be distributed and written instructions reviewed. In addition, all groups will be instructed to continue using the acclimation products per acclimation instructions. Subjects will be sent home with copies of questionnaires, their assigned kit box, the product diary, and the standardized snack. While at home, subjects will complete the Baseline MD questionnaire over the phone with site staff. Subjects will then use their assigned product for the first time and then a timer will be set for 6 hours. Immediately following the product use, subjects will complete the Immediate MD Questionnaire over the phone with site staff. Site staff will contact the subjects at home at the corresponding timepoints for completing the remaining questionnaires, (the PPAQ I/ MD 30-minute Questionnaire, the PPAQ I/ MD 1-hour, 2-hour, 4-hour and 6-hour Questionnaires).

Subjects will be instructed to refrain from eating, drinking, smoking, using their test products, using tobacco, using a medicated lozenge, chewing gum, or breath mints during the 6-hour test period. Subjects may consume their provided standardized snack immediately after the 4-hour questionnaire.

Should a subject not be able to follow the drinking or eating restrictions for the full six hours (i.e. require a rescue product such as water), the subject will be asked to fill out the next set of questionnaires, and then they will be allowed to resume normal activity for the rest of Day 1. Site staff will record the time the subject completed the questionnaires in General Comments. If desired, the subject will be allowed to remain in the study.

After the 6-hour questionnaire, subjects will be reminded to adhere to their assigned product use instruction sheet for the duration of the study. Subjects will be asked to complete the product diary tracking their product usage and water intake. Subjects from all groups will be allowed to sip water as needed on Days 2 – 7. Subjects will be reminded to bring their acclimation and treatment kit boxes and completed product diary to their next study visit.

Day 8 (Visit 3)
The night before this study visit, subjects will be reminded to complete the PPAQ II Questionnaire immediately after waking up in the morning (before eating, drinking, brushing their teeth, chewing gum or smoking). Subjects will also be reminded to adhere to their assigned treatment instruction sheet prior to coming to the site.

At the site, continuance criteria will be assessed. The completed PPAQ II will be collected and subsequently transcribed into the database by site staff (acclimation kit boxes may be collected at this visit). An Oral Examination will be performed. After the oral exam, subjects will be sent home with copies of questionnaires, their assigned kit box, the product diary, and the standardized snack. While at home, subjects will use their assigned product and notify site staff, and then a timer will be set for 6 hours. Subjects will complete the PPAQ I 30-minute Questionnaire, the PPAQ I 1-hour, 2-hour, 4-hour and 6-hour Questionnaires over the phone with site staff.

Subjects will be instructed to refrain from eating, drinking, smoking, using their test products, using tobacco, using a medicated lozenge, chewing gum, or breath mints for the during the 6-hour test period. Subjects may consume the provided standardized snack immediately after the 4-hour questionnaire. After completing the 6-hour questionnaires, the subject will be given instructions from site on how to return study products and product diary. The subject will then be dismissed from the study, and a Subject Accountability form will be completed.

Should a subject not be able to follow the drinking or eating restrictions for the full six hours (i.e. require a rescue product such as water), the subject will be asked to fill out the next set of questionnaires. Site staff will record the time the subject completed the questionnaires in General Comments. The subject will then be dismissed from the study.

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

General Comments and Adverse Events
General comments can be recorded at any time during the study. Any AE will be documented in ECRF. Any self-reported AE that remains unresolved by the end of the study should be followed up until resolution by the investigator/designee, and the resolution should be documented only as source documentation. If a subject is unreachable to determine whether the AE has been resolved, the attempts to contact the subject should be documented as source documentation. Examiner observed AEs that are unresolved at the end of the study are followed to resolution at the discretion of the Medical Monitor.

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;
- Sign a Confidentiality Disclosure Agreement (CDA) form and be given a signed copy;
- Be at least 18 years of age;
- Agree not to participate in any other oral care studies for the duration of this study;

- Agree to delay elective dentistry, including dental prophylaxis, until study completion, and to report any non-study dentistry received during the course of the study;
- Agree to refrain from the use of any non-study oral hygiene products for the study duration including mouth rinse and toothpaste (flossing is permitted if part of their normal routine);
- Self-report a dry mouth feeling according to the modified DMI questions (Subject must answer at least 2 out of 4 questions with 'agree a little,' 'agree' or 'strongly agree');
- Agree to refrain from eating, drinking, smoking, using oral care products, using tobacco, using a medicated lozenge, chewing gum, or breath mints during the 6-hour test period (except snack after 4-hour Questionnaire);
- Agree to return for all scheduled visits and to follow all study procedures.

5. Exclusion Criteria

Subjects will be excluded from study participation where there is evidence of:

- Any condition or disease, as determined by the Investigator/Designee, that could be expected to interfere with examination procedures, with compliance, or with the subject's safe completion of the study;
- Severe periodontal disease, as characterized by purulent exudate, generalized mobility, and/or severe recession;
- Active treatment for periodontitis;
- Having a history of allergies or hypersensitivity to mouth rinse or ingredients in commercial dental products or cosmetics;
- Self-reported pregnancy or the intent to become pregnant during the study, or breast feeding;
- Full or partial dentures or any orthodontic appliances such as braces or aligners, or tongue or mouth piercing;
- Inability to undergo any study procedure;
- Having untreated oral mucosal disease which in the opinion of the investigator could interfere with the study (e.g., current oral ulceration); or
- Evidence of gross intra-oral neglect or need for extensive dental therapy.

6. Continuance Criteria

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

- Have participated in any other oral care study since the last study visit;
- Since the last study visit, have developed any condition or disease or taken a new medication, which as determined by the Investigator/Designee could be expected to interfere with examination procedures, with compliance, or with the subject's safe completion of the study;
- Used any non-study oral hygiene products since the last study visit;
- Used study mouth rinse prior to the study visit (*Day 8 only*); or
- Had any non-study dentistry, including dental prophylaxis, performed since the last study visit.

7. Identity of Investigational Product(s)

- Acclimation/Washout: Burt's Bees Enamel Care Toothpaste (0.243% sodium fluoride, 0.13% w/v fluoride ion) and an Oral-B Indicator toothbrush
- Experimental Rinse Group: Burt's Bees Enamel Care Toothpaste (0.243% sodium fluoride, 0.13% w/v fluoride ion), Experimental mouth rinse (0.1% Sodium Hyaluronate), and an Oral-B Indicator toothbrush
- Positive Control Group: Burt's Bees Enamel Care Toothpaste (0.243% sodium fluoride, 0.13% w/v fluoride ion), GUM® Hydral Dry Mouth Relief daily oral rinse, and an Oral-B Indicator toothbrush
- Water Control Group: Burt's Bees Enamel Care Toothpaste (0.243% sodium fluoride, 0.13% w/v fluoride ion), 15ml of water and an Oral-B Indicator toothbrush

8. Product Usage

At-home brushing

Subjects will brush their teeth thoroughly, twice daily (morning and evening) as they normally do with the provided toothpaste and toothbrush. Subjects will be asked to use this toothpaste and toothbrush for the duration of the study, for both the acclimation and treatment period. Flossing and tongue brushing are permitted during the study if it is part of their normal routine.

Experimental Rinse Group

Day 1 and Day 8 first use: Subjects will rinse with 15ml of mouth rinse for 30 seconds. Subjects will record usage in their product diary. Subjects will not be allowed to use any mouth rinse during the 6-hour time period on Baseline/Day 1 and Day 8.

After first use Day 1- Day 7: Subjects will be instructed to use the rinse product (15ml for 30 seconds) at least twice a day, up to 5 times a day. The rinse can be used alone or after each brushing. Subjects will record all usage in their product diary.

Positive Control Group

Day 1 and Day 8 first use: Subjects will rinse with 15ml of mouth rinse for 30 seconds. Subjects will record usage in their product diary. Subjects will not be allowed to use any mouth rinse during the 6-hour time period on Baseline/Day 1 and Day 8.

After first use Day 1 – Day 7: Subjects will be instructed to use the rinse product (15ml for 30 seconds) at least twice a day, up to 5 times a day. The rinse can be used alone or after each brushing. Subjects will record all usage in their product diary.

Water Control Group

Day 1 and Day 8 first use: Subjects will rinse with 15ml of water for 30 seconds. Subjects will record usage in their product diary. Subjects will not be allowed to use any water rinse during the 6-hour time period on Baseline/Day 1 and Day 8.

After first use Day 1 – Day 7: Subjects will be instructed to rinse with water (15ml for 30 seconds) at least twice a day, up to 5 times a day. The rinsing can be used alone or after each brushing. Subjects will record all usage in their product diary.

Subjects from all groups will be allowed to sip water as needed on Days 2 – 7, water intake should be captured in their product diaries.

9. Blinding, Labeling, and Shipping Plan

Acclimation take-home kit boxes will be labeled with study number, emergency phone number, distributor name/address, appropriate caution statements, content statement and other information as required by internal regulations and clinical SOPs. Treatment take-home kit boxes will be identically sized and labeled with a unique kit box number or code, study number, emergency phone number, distributor name/address, appropriate caution statements, content statement and other information as required by internal regulations and clinical SOPs. The shipping containers will be labeled with the clinical site address and a content statement listing study number and kit box numbers contained within. The site will be provided with supplemental product.

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 or treatment code 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 subject's 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 a clinically serious AE

occurs or management of the subject requires knowledge of the identity of the investigational product. The 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.

10. Method of Assigning Subjects to Treatment Groups

Study Design	n	n/group	B&A Program	PRA Block Size	Strata	Cut-offs*	Cohab
Parallel	150	50	Yes	3	DMI Severity Score; Age	Mild (2-5), Moderate (6-8), Severe (9-12); <=54, >54	Yes

B&A Program

At the Baseline visit, subjects will be randomly assigned to one of the three treatment groups (up to 50 per group) using an encoded B&A program supplied by the Sponsor. The subjects will be stratified based on DMI Severity Score and age. Subjects residing in the same household will be assigned to the same treatment group.

11. Determination of Sample Size

Forty-five subjects per treatment group completing the study will ensure 80% power to detect a difference of at least 0.66 units on the 5-points PPAQ 1 scale in the Positive Control or Experimental rinse relative to water with a standard deviation of 1.1, in one-sided testing at a 2.5% significance level (based on published research). A target of up to 50 subjects will be recruited per group (total of up to 150) allowing for a 10% dropout rate.

12. Efficacy Variables

DMI Questionnaire

The following set of questions will be asked at the Acclimation (Visit 1).

(Severity Score = sum of 4 questions where: strongly disagree= -2, disagree= -1, disagree a little=0, agree a little=1, agree=2, strongly agree=3). Subjects to answer 2 or more of the 4 questions below positively in order to continue into the study. For summing the DMI score for randomization purposes, negative scores (strongly disagree= -2, disagree= -1) will be calculated as 0 in the database.

How much do you agree or disagree that you experience the following? (strongly disagree, disagree, disagree a little, agree a little, agree, strongly agree)

1) No moisture in the mouth
2) Lips sticking to teeth
3) Tongue sticking to roof of mouth
4) Throat feels dry

Baseline MD Questionnaire

The following set of questions will be asked at Baseline/Day1 (Visit 2).

Subjects to answer:

1) How moist does your mouth feel now? (0=not at all to 10=very moist)
2) How dry does your mouth feel now? (0=very dry to 10=not dry at all)

Immediate MD Questionnaire
The following set of questions will be asked at Baseline/Day1 (Visit 2).

Subjects to answer:
1) How moist does your mouth feel now? (0=not at all to 10=very moist)
2) How dry does your mouth feel now? (0=very dry to 10=not dry at all)

PPAQ I/ MD Questionnaire
The following set of questions will be asked at Baseline/Day1 (Visit 2) – 30 minutes, 1-hour, 2-hour, 4-hour, 6-hour.

Since you have been using the product, please rate each of the following at this timepoint: (Select one response for each attribute)- excellent=5, very good=4, good=3, fair=2, poor=1:
1) Relieves the discomfort of your dry mouth
2) Feels comfortable in your mouth
3) Soothes your mouth
4) Allows you to speak without difficulty
5) Effectively moistens your mouth
6) Effectively lubricates your mouth
7) Helps to freshen your breath
8) Protects your mouth from drying out
9) Provides whole mouth comfort
10) Helps you to swallow without difficulty
11) Helps your mouth feel “normal”

Subjects to answer:
1) How moist does your mouth feel now? (0=not at all to 10=very moist)
2) How dry does your mouth feel now? (0=very dry to 10=not dry at all)

PPAQ II Questionnaire
The following set of questions will be answered at home before Day 8 (Visit 3).

Since you have been using the product over the last 8 days, please rate each of the following as they apply to the rinse study product: (Select one response for each attribute)- excellent=5, very good=4, good=3, fair=2, poor=1:
1) Provides relief all night
2) Reduces the number of times you wake up from dry mouth
3) Feeling less parched when you wake up
4) Having a long-lasting dry mouth relief
5) Having a long-lasting lubricating effect
6) Having a long-lasting moisturizing effect

PPAQ I Questionnaire
The following set of questions will be asked at Day8 (Visit 3)- 30 minutes, 1-hour, 2-hour, 4-hour, 6-hour.

Since you have been using the product, please rate each of the following at this timepoint: (Select one response for each attribute)- excellent=5, very good=4, good=3, fair=2, poor=1:
1) Relieves the discomfort of your dry mouth
2) Feels comfortable in your mouth
3) Soothes your mouth
4) Allows you to speak without difficulty
5) Effectively moistens your mouth
6) Effectively lubricates your mouth
7) Helps to freshen your breath
8) Protects your mouth from drying out

9) Provides whole mouth comfort
10) Helps you to swallow without difficulty
11) Helps your mouth feel "normal"

13. 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 are conducted via a visual examination of the dentition and restorations utilizing a standard dental light, dental mirror, and air syringe. All abnormal findings are recorded and categorized by their location with hard tissue findings categorized as "other-oral." An AE is recorded if a new abnormal finding is noted after treatment application or any abnormal finding noted prior to treatment application increases in severity after treatment is applied.

14. Hypotheses

The following hypotheses will be tested using a serial gatekeeping approach as specified below (Multiple Testing Problems in Pharmaceutical Statistics, Chapter 5: Gatekeeping Procedures in Clinical Trials, editors A Dmitrienko, AC Tamhane, F Bretz, Chapman and Hall 2010.)

The primary endpoint will be the response to "relieving the discomfort of dry mouth" from the modified PPAQ I.

For model sensitivity Hypothesis 1 will be tested at Hour 4 at Day 1:

Hypothesis 1
Null: The mean response for the Positive Control Rinse is less than or equal to the mean response for the Water Control.
Alternative: The mean response for the Positive Control Rinse is greater than the mean response for the Water Control.

If the Null Hypothesis is rejected for Hypothesis 1 then Hypotheses 2 will be tested for Hour 4 at Day 1:

Hypothesis 2
Null: The mean response for the Experimental Rinse is less than or equal to the mean response for the Water Control.
Alternative: The mean response for the Experimental Rinse is greater than the mean response for the Water Control.

If the Null Hypothesis is rejected for Hypothesis 2 then Hypotheses 3 will be tested for Hour 6 at Day 1:

Hypothesis 3
Null: The mean response for the Experimental Rinse is less than or equal to the mean response for the Water Control.
Alternative: The mean response for the Experimental Rinse is greater than the mean response for the Water Control.

15. Statistical and Analytical Plans

Analysis Population

Efficacy analysis will be conducted on the Intent-to-treat (ITT) population, defined as those subjects who received study treatment and have at least one post-treatment efficacy measurement. This will be the primary population for the efficacy analysis.

Subjects who require "rescue product" will complete the questionnaire at the time of rescue. These responses will then be carried forward to all subsequent timepoints for that day for purposes of statistical analyses. No imputation for other missing data will be performed unless more than 10% of data are missing. If more than 10% of data are missing, the last observation will be carried forward for that day for purposes of statistical analyses.

Efficacy Analyses

Summary statistics (e.g., means, standard deviations, frequencies, etc.) of the demographic characteristics and questionnaire responses will be calculated for each treatment group and applicable time points.

For the primary comparisons, the treatment groups will be compared using the analysis of covariance method with the response to "relieving the discomfort of dry mouth" from the modified PPAQ I as the response and DMI severity score, response to "how moist does your mouth feel right now" at baseline, or response to "how dry does your mouth feel right now" at baseline may be used as the covariates. Statistical comparisons will be one-sided with a significance level of 0.025.

$$Y_{i1} = \mu + \alpha \cdot Covariate_i + \beta \cdot Group_i + \epsilon_i$$

The secondary endpoints of interest will be the responses to "how moist does your mouth feel right now" and "how dry does your mouth feel right now" from the MD questionnaire immediately after use at Day 1. The Experimental rinse group will be compared to water using the analysis of covariance method with the immediate score as the response and DMI severity score and baseline response may be used as the covariates.

Responses to all other questions and time points will be of tertiary interest. Additional analyses of the data may be performed.

Safety Analyses

Adverse events will be summarized overall and by treatment group.

APPENDIX

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.

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 is 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.