

Study Title: An Evaluation of the Efficacy of 3M™ Dry Mouth Moisturizing Spray on the Relief of Dry Mouth Symptoms

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Study Number and Protocol Title	An Evaluation of the Efficacy of 3M™ Dry Mouth Moisturizing Spray on the Relief of Dry Mouth Symptoms
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Investigator Study Documentation File (Regulatory Binder)

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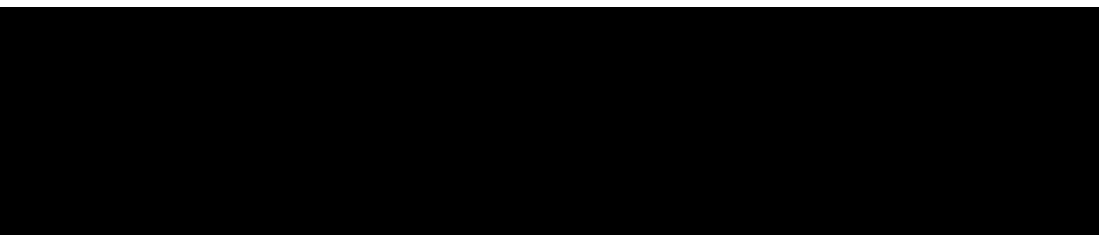
1. Background Information

1.1 Name, Description and Intended Use of the Experimental Material

Xerostomia is a subjective sensation of dryness of the mouth. Dry mouth can be a symptom or a side effect of other conditions (e.g., diabetes, hypertension, Sjögren's syndrome, stroke). It is also a common side effect of many prescription and nonprescription drugs; including drugs used to treat hypertension, depression, anxiety, allergies, and colds (decongestants and antihistamines).

Mouth dryness is commonly associated with oral symptoms such as taste disturbances, bad breath and painful mouth ulcers. Dry mouth can also affect oral functions such as speech, chewing, and swallowing.^{1,2}

Management includes symptomatic relief and prevention or correction of the sequelae of saliva hypofunction, and treatment of any underlying disease. Adequate hydration of the oral tissues (frequent sips of water) is the standard treatment of xerostomia.^{3,4} Several over-the-counter products (e.g., Biotène®) are also available for treating dry mouth symptoms; however, data collected during 3M-hosted focus groups and voice of customer activities indicated that there continues to be an increasing demand for effective dry-mouth relief products. For this reason, 3M's Oral Care Solutions Division plans to expand their prevention portfolio and has been developing an oral spray solution, which is intended to be used to relieve dry mouth symptoms in persons with Xerostomia.



The purpose of this clinical trial is to evaluate and validate the performance of the experimental mouth spray when used by persons with mild to severe dry mouth symptoms. This study is designed to gather data from these individuals regarding their opinions about the product's performance, mouth-feel qualities, and user's willingness to purchase the product when it becomes commercially available.

We hypothesize that the use of 3M™ Experimental Dry Mouth Moisturizing Spray will be non-inferior to Biotène (GSK) in alleviating dry mouth symptoms.

1.2 Summary of Previous Studies



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[REDACTED]

To determine the preliminary flavor selections for the mouth spray, a food product development and research company (Merlin Company, Plymouth, MN) was employed. They helped in the development of the flavored formulations and conducted various taste panel evaluations with professional taste testers to select and optimize the flavored formulations.

Subsequent to Merlin's evaluators making their favorite flavor choices it was necessary to confirm the flavored formulations in a xerostomia population. Clinical trials were conducted [REDACTED] in [REDACTED] healthy [REDACTED] volunteers, with self-reported moderate to severe dry mouth, to test the prototype formulations. Two clinical trials were conducted:

- The first study was based solely on spoon delivery of 4 individual prototype formulations to gather taste/flavor preferences to narrow down the flavor options for the final product flavor. The formulations were compared to 2 commercial dry mouth spray formulations.
- The second study was conducted using a spray delivery system to identify the final flavors and to gather preliminary data for immediate dry mouth relief, mouth feel of formulation, and usability compared to Biotène.

1.3 Risk/Benefit Summary

Risks:

3M™ Dry Mouth Moisturizing Spray is a surface device with limited contact duration per use. As it will be used by subjects with mild to severe xerostomia, some degree of contact on breached or compromised oral mucosa is expected. Therefore, the relevant ISO 10993, ISO 7405, USFDA, and Japan medical device evaluation guidance were used in establishing the study design. Subject with breached or compromised oral surfaces will evaluate the product for >30 days.

A Diplomate of the American Board of Toxicology has assessed the safety of the experimental sample, 3M™ Dry Mouth Moisturizing Spray. Standard risk assessment techniques and consideration of internationally recognized guidelines were used in this evaluation. The experimental sample, 3M™ Dry Mouth Moisturizing Spray is safe for human use in this clinical evaluation based on the following considerations:

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- 1) All of the ingredients in the product are used in food; and
- 2) A review of the product ingredient hazards in relation to the exposure during the clinical trial

This prototypic device 3M™ Dry Mouth Moisturizing Spray is associated with minimum risks.

Risk Minimization

Efforts to minimize risks to study subjects will be made with the following approaches:

- Compliance with ISO 10993
- Selection of investigators who are experienced dental clinicians
- Clearly defined inclusion and exclusion criteria will be used to ensure only appropriate subjects are enrolled
- Ensuring that treatment and follow-up of subjects is consistent with current dental practice
- Monitoring of investigational sites and patients
- Review of reported Adverse Events

Based on the biocompatibility and a general risk review, the possible side effects of using the experimental device include:

- Potential stinging or burning sensations associated with the product
- Sloughing of the superficial soft tissues in the oral cavity such as the inside surface of the cheeks
- Paresthesia (local numbing for a short period of time)
- Soft tissue erythema and edema
- The product could accidentally be splashed into the eye and minor, limited irritation may occur
- Allergic reaction to the product

Benefits: There may be no direct benefits to the participants in this study. However, information obtained in this investigation may benefit others in the future.

1.4 Investigational Material Application

Experimental material will be dispensed by the subject to their own mouth by using a spray bottle to deliver the oil-in-water emulsion into the mouth.

1.5 GCP and Regulatory Requirements

The 3M™ Dry Mouth Moisturizing Spray is a medical device (unclassified). 3M Company (Maplewood, MN) has determined this product is a non-significant risk

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device, based on biocompatibility testing and the 2 taste studies conducted on 3M Healthy Volunteers, which had no adverse events reported. This study will be conducted in compliance with this protocol and GCP including 45 CFR 160 & 164 (Authorization for Use/Disclosure of PHI), 21 CFR 50 (Informed Consent) and 56 (IRBs). The experimental device will be used in a manner consistent with its intended use, and abbreviated CFR 21 FDA §812.2 regulation applies. The device will be registered with the FDA as an unclassified medical device in 2020, subject to 510(k) regulatory pathway based on clearance. It is similar to a previously registered predicate medical device called Biotène® Moisturizing Mouth Spray (510(k) number K123731, K103745).

Prior to FDA approval, a Human Subjects' Protection Board (IRB) serves as a surrogate to the FDA in making a nonsignificant risk determination for review, approval, and continuing review in device-related studies.

A non-significant risk device study may start at the institution as soon as the IRB reviews and approves the study. Progress reports or final reports to FDA and an IDE application to the FDA are not required.

1.6 Study Population

Adults that meet the inclusion/exclusion criteria.

2. Study Objectives and Purpose

The purpose of this study is to investigate the efficacy of 3M™ Dry Mouth Moisturizing Spray to reduce symptoms of dry mouth for up to 4 hours and after 7 days of use. In addition, this study aims to support comparative claims.

3. Study Design

3.1 Study Type

The proposed study will be a controlled randomized cross-over design. This study will compare 3M™ Dry Mouth Moisturizing Spray to commercialized device (active control) and water (inactive control) to determine the effect and changes in the effect over time, in subjects experiencing dry mouth symptoms.

3.2 Primary and Secondary Endpoints

The primary endpoint of this study is reduction in mouth dryness at 15 minutes after 1 dose of 3M™ Dry Mouth Moisturizing Spray.

We hypothesize that the use of 3M™ Dry Mouth Moisturizing Spray will be non-inferior to GSK Biotène® Moisturizing Mouth Spray (Biotene) in alleviating mouth

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dryness as assessed by the Visual Analog Scale for the duration of 15 minutes after 1 dose.

The secondary endpoints are to:

- Mouth dryness evaluated using a Visual Analog Scale, at 5-, 30-, 60-, 120- and 240-minutes post 1 dose of use to determine whether 3M™ Dry Mouth Moisturizing Spray is equally effective to the prototype Biotène® control.
- Evaluate the clinical safety of the 3M Dry Mouth Moisturizing Spray.
- Determine product usability, acceptability and preference using patient questionnaires.
- Compare 3M™ Dry Mouth Moisturizing Spray to Biotene® and water.

3.3 Randomization and Blinding

All subjects completing the wash-in procedures and meeting inclusion/exclusion criteria will undergo a pre-study 5-hour visit (the day before randomization) to assess the effect of water on their dry mouth symptoms. The subjects will return the next day for confirmation that inclusion/exclusion criteria and the wash-in procedures continue to be met or followed. Eligible subjects will be randomized at this baseline visit in a 1:1 ratio to one of two treatment orders: A->B (AB) or B->A (BA). The order of product usage will be assigned in sealed envelopes created from a randomization schedule generated by the study statistician.

Due to the obvious differences in products and the dispensing spray bottles, blinding of subject to treatment order will not be possible. In addition, no attempt will be made to blind subjects when given a single dose of water the day before randomization.

All clinical oral examinations performed post-randomization will be conducted with the evaluator blinded to subject's product use assignment. Subjects will be instructed to avoid discussing their assigned product with the evaluator.

3.4 Study Materials and Labeling

3M™ Dry Mouth Moisturizing Spray formula is an oil-in-water emulsion. The oil phase provides comfort to the oral mucosa. The water phase is buffered at a neutral pH using a phosphate buffering system, and is sweetened with non-cariogenic sugars including xylitol, erythritol and sucralose. 3M Dry Mouth Moisturizing Spray will be applied to the oral mucosa as needed for the relief of dry mouth symptoms. Components are of food or compendial grade. The instructions for use are provided as Appendix B.

- Treatment [A]: 3M™ Dry Mouth Moisturizing Spray
- Treatment [B]: Control - Biotène® Moisturizing Mouth Spray
- Treatment [C]: Control – Bottled water

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3.4.1 Investigational Material Labeling

3M will label, package and ship the study materials to the research facility. Each experimental material will be labeled with the following minimum information:

For use in Study EM-11-050038 only
3M Health Care, St. Paul, MN 55144-1000
Identifying lot or control number
Study Material name or code designation:
Quantity of contents
Expiration date:
“Use as directed”
Storage conditions: Store at room temperature.
If you have questions, call 909-558-8069.

3.4.2 Other Material Labeling

Biotene® is a commercially available product. It will be over labeled with the following:

For use in Study EM-11-050038 only
3M Health Care, St. Paul, MN 55144-1000
Identifying lot or control number
Study Material name or code designation:
Quantity of contents
Expiration date:
“Use as directed”
Storage conditions: Store at room temperature.
If you have questions, call 909-558-8069.

Bottled water will be labeled with Sample C.

3.5 Study Duration

The anticipated duration of this clinical study from enrollment of first subject to treatment of final subject is 3- to 6 months.

Each participant's time commitment to this research project will be 90 minutes at first visit (screening and enrollment/start of wash-in). On the 2nd visit (water only evaluation) an Oral Exam and Challacombe assessment will be completed prior to dosing. If the Challacombe score is 0, then the subject will not be enrolled, and the time commitment will be up to 90 minutes. If the Challacombe score is 1 or greater, subject will complete to the 5-hour water-only evaluation. On the 3rd visit (baseline period 1) the Challacombe assessment will be re-checked to ensure it is still ≥ 1 . If

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the subject still meets all the other inclusion/exclusion criteria, the subjects will be randomized into the treatment phase of the study.

Enrolled subjects will be scheduled for 2 additional 5-hour visits and two 60-minute visits. There is also at least a 2-day wash-in period prior to any sample dosing and at least a 2-day wash-out period between 1st and 2nd study periods. Each individual subject will participate in the study for total time of up to 4 weeks. There is the possibility that a subject may develop a study related adverse event during participation. Should this happen, a detailed description of start date and other pertinent information will be recorded on an adverse event form and the subject's continued participation in the study and treatment will be at the Investigator's discretion.

All subjects experiencing an adverse event will be followed until the adverse event is resolved.

Visit	Pre-treatment Phase			Treatment Phase				
	Screening	(wash-in period)	Water-only Evaluation	Baseline Period 1	End of Treatment Period 1	(wash-out period)	Baseline Period 2	End of treatment Period 2 (End of study)
	Start of wash-in							
	Description/sub-phase							
	Study Day		-1	0	7		9+	16+
Length of Time		>=2 days			>= 2 days			

3.6 Study Termination/Subject Discontinuation or Withdrawal/Subject Revocation of Authorization

3.6.1 Study Termination

3M or the Investigator has the right to terminate or suspend the study at any time for medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

3.6.2 Subject Discontinuation

The Investigator may discontinue individual subjects from the study at any time. Subjects may voluntarily withdraw from the study at any time. The Investigator will provide a written report on the appropriate CRF describing the date and reason for discontinuance.

A subject who is discontinued or voluntarily withdraws will not be replaced.

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3.6.3 Subject Revocation of Authorization to Use and Disclose PHI

In order to implement a valid revocation of authorization, the subject or their representative must make the request in writing to the Loma Linda University School of Dentistry, Chan Shun Pavilion, CSP-A1010, 11175 Campus Street, Loma Linda, CA 92350, to the attention of the PI. The revocation cannot stop the use or disclosure of information that has been collected prior to the revocation, is needed to ensure complete and accurate study results, is required by law or government regulation (e.g., reporting adverse events, etc.). Revocation of an authorization may not be used to withhold normal medical care from the subject but will make the subject ineligible to receive the study treatment or care.

3.7 Investigational Material Accountability

3M™ always requires Investigators to maintain accountability and adequate inventory security of the experimental material at all times. The Investigator or designee will:

- Complete a Confirmation of Release and Receipt of Clinical Supplies form and maintain and account for inventory on the Investigational Material Disposition form.
- Keep experimental materials in a secure storage area, accessible only to authorized individuals.
- Dispense experimental material only to subjects properly enrolled into the study.
- Return all unused experimental materials to 3M at the end of the study or dispose of as agreed upon.

3.8 Randomization and Blinding

The cross-over order of treatments will be assigned using sealed randomization envelopes. Order assigned will be either A->B (AB) or B->A (BA). The Investigator or their designated staff member is responsible to assure that the study randomization is followed. Subjects randomized will have their data and records numbered with the assigned numbers 001 to 040. Study treatment materials will be labeled with the appropriate codes. The 3M study monitor must be notified within 24 hours of any emergency deviation from protocol related to randomization errors.

3.9 Source Data

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Data will be written on data collection sheets and then entered into the electronic data capture (eDC) database by research staff, the paper is then considered source data. The data entry should occur within a week of collection and copies of the data sheets should be sent to sponsor. Subject will be keeping a diary, this is considered source data, and will be returned to the research staff and transferred to the sponsor for data entry within a week of the return of the diary to the research staff. Completed paper data collection sheets and eCRFs will be reviewed by the site monitor to ensure accuracy and consistency of subject data. Any discrepancies found during CRF review are to be clarified by the Investigator or designee. Investigator must keep physical CRFs in the study subject binder for a minimum of 2 years after completion of the study.

3.10 Protocol Modifications

3.10.1 Protocol Amendments

The party initiating an amendment must confirm it clearly in writing using the Amendment/Administrative Revision form. It must be signed and dated by 3M and, in the case of a significant amendment, the Investigator. A significant amendment means one that affects the safety, rights or welfare of subjects, the scope of the investigation or the scientific quality of the study.

3M will notify the Investigator when a protocol amendment may be implemented.

3.10.2 Protocol Deviations

A deviation is a departure from the protocol that will likely affect the safety, rights or welfare of subjects, the scope of the investigation or the scientific quality of the study.

A protocol deviation is only for an individual subject. Protocol deviations are documented on a Protocol Deviation Form or appropriate CRF.

Deviations that potentially affect 1) subject safety, rights or welfare, 2) data integrity or 3) compromise the statistical analysis of the study require immediate communication to 3M. The Investigator must contact the 3M study monitor within 24 hours of occurrence at the following phone number: 651-737-0263.

A Protocol Deviation Form must be completed by the Investigator and include the type of deviation and a description of the circumstances surrounding the deviation. A copy is sent to the 3M study monitor within 24 hours of identifying the occurrence.

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Deviations which are made to protect the life or physical well-being of a subject in an emergency must be reported to the IRB within 5 working days after 3M learns of the occurrence.

The major protocol deviations include subjects missing the primary endpoint visit for one or both treatment periods, subjects not taking product for one or more days, and subjects taking excluded medications (any non-study assigned dry mouth alleviating products).

3.11 Computerized Systems

All statistical analyses will be conducted using SAS software. Clindex will be used for electronic capture of study data. Electronic study documents will be stored in ENOVIA. Any additional computerized systems used in the conduct of this study will be identified in the study report.

4. Subject Selection

4.1 Subject Inclusion Criteria

Screening – Start of Wash-In Visit

- Subject who is ≥ 18 years of age and complains of dry mouth
- Only 1 subject per household is allowed into study
- Subject with a Challacombe scale score of 1 or higher
- Subject agrees to refrain from eating spicy foods and foods containing garlic beginning 48-hours prior to all study visits
- Subject agrees to eat a meal prior to all study visits that include sample evaluation in the clinic
- Subject agrees to not eat, drink, chew tobacco, chew gum, smoke, brush or floss teeth for 2-hours prior to sample evaluation study visits
- Subject agree to not use any oral care products and any type of breath mint or lozenges for 2-hours prior to sample evaluation study visits
- Subject agrees to refrain from any food and liquid during the 5-hour study visits except for what is provided by the study research staff (e.g., water and treatments A and B during evaluation periods)
- Subject agrees to only use those clinical oral care supplies provided during the entire study
- Able to understand and willing to sign the Informed Consent Form

Water Only Evaluation Visit

- Subject has successfully completed a ≥ 2 -day wash-in period
- Subject has Challacombe scale score of 1 or higher

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- Subject has refrained from eating spicy foods and foods containing garlic beginning 48-hours prior to the sample evaluation visits
- Subject ate a meal prior to sample evaluation study visits
- Subject has not eaten, drank, chewed tobacco, chewed gum, smoked, brushed or flossed teeth for 2-hours prior to sample evaluation study visits
- Subject has not used any oral care products, any type of breath mint or lozenges for 2-hours prior to sample evaluation study visits
- Subject agrees to refrain from any food and liquid during the 5-hour study visits except for what is provided by the study research staff (e.g., water and treatments A and B during evaluation periods)
- Subject has used only those clinical oral care supplies provided during study

Baseline Period 1/Randomization Visit

- Subject has successfully completed a ≥ 2 -day wash-in period
- Subject has a Challacombe Scale score of 1 or higher
- Subject has refrained from eating spicy foods and foods containing garlic beginning 48-hours prior to sample evaluation study visits
- Subject ate a meal prior to sample evaluation study visits
- Subject has not eaten, drank, chewed tobacco, chewed gum, smoked, brushed or flossed teeth for 2-hours prior to sample evaluation study visits
- Subject has not used any oral care products and any type of breath mint or lozenges for 2-hours prior to sample evaluation study visits
- Subject agrees to refrain from any food and liquid during the 5-hour study visits except for what is provided by the study research staff (e.g., water and treatments A and B during evaluation periods)
- Subject has used only those clinical oral care supplies provided during study

4.2 Subject Exclusion Criteria for Start of Wash-In, Water Only Evaluation and Baseline Period 1 (Randomization Visit)

- Subject has active mouth sores (e.g., cold sores, cuts, burns, canker sores)
- Subject has a life-threatening pathological condition
- Subject is participating in another clinical trial at the time of the study
- Subject has profound marginal periodontal disease (purulent exudate, tooth mobility, and/or extensive alveolar bone loss)
- Medical and oral conditions that, in the investigator's judgment, may compromise the subject's safety or interfere with the conduct and outcome of the study
- Difficult to be compliant with recalls, such as extensive travel commitments, lack of transportation etc.

4.3 Subject Consent

The Principal Investigator or qualified Co-Investigators mentioned above are responsible for protecting patient confidentiality when discussing the study

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details. The potential subject will have as much time to make a decision about participation in the study as they need to ensure that they understand everything within the consent document. The Investigator must ensure that written informed consent to participate in the investigation is obtained before including any individual as a subject in the investigation. Written informed consent will be obtained after the aims, methods, anticipated benefits, and potential hazards are explained and each subject's questions have been answered. The Investigator must provide the prospective subject or their representative sufficient opportunity to consider whether or not to participate and minimize the possibility of coercion or undue influence. The process is designed to 1) give the subject all the information that they need, 2) ensure that the subject understands the information and 3) give the subject a chance to consider study participation. The process should permit the subject to ask questions and exchange information freely.

Specifically, the Investigator is to explain to each subject all elements of informed consent as specified in 21 CFR 50.25. After the explanation, the subject or representative will voluntarily sign and date the consent form if they wish to participate in the study. A copy of the consent form must be provided to the subject. A signed and dated copy of the consent form must be maintained in the Investigator study documentation file at all times. Consent and study participation, with date, must be documented in the patient record/chart.

Photographs will be taken of some of the subjects for non-diagnostic, publication and/or research development purposes. Of those subjects initially photographed, they will be followed throughout the study with photographs at each visit. For any extreme outcomes or outcome of interest to the investigator, subject photographs will be taken at any time throughout the study.

4.4 Subject Authorization for Use and Disclosure of Protected Health Information (PHI)

The Investigator must ensure that written authorization for use and disclosure of protected health information is obtained before including any individual as a subject in the investigation. Written authorization for use and disclosure of protected health information is combined with the consent form (e.g., compound authorization) and must be obtained by the Investigator prior to including any individual as a subject in the investigation.

Specifically, the Investigator is to explain to each subject all elements of authorization as specified in 45 CFR 164.508. After the explanation, the subject or representative must voluntarily sign and date the authorization form if they wish to participate in the study. A copy of the authorization form must be provided to the subject. A signed and dated copy of the authorization form must be maintained in the

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Investigator study documentation file at all times and may be placed in the patient's medical record.

An authorization form may be combined with a consent form (e.g., compound authorization) if required by the IRB. All required elements for both informed consent and authorization must be included in a compound authorization.

5. Treatment of Subjects

5.1 Treatment(s) to be Administered

Visit 1 – Screening Visit/Start of Wash-In

1. The subject signs the study consent form and authorization form.
2. A study examiner will perform an oral exam and perform an assessment using the Challacombe-Scale to determine the severity level of dry mouth prior to any dosing. If the Challacombe score is 0, then the subject will not continue with study participation. If the Challacombe score is 1 or greater, subject will be enrolled.
3. Participants will be qualified using the inclusion/exclusion criteria set forth in this protocol.
4. Participant's medical history will be collected and recorded.
5. Subject will be instructed for how to perform at least a 2-day wash-in period.
6. Subject will be given clinical study oral care supplies.
7. The participant will be scheduled for a 5-hour appointment.

Visit 2 - Water Only Evaluation Visit

1. Confirm that subject still meets the inclusion/exclusion criteria set forth in this protocol.
2. Confirm there were no changes to medications.
3. A study examiner will perform an oral exam and perform an assessment using the Challacombe-Scale to determine the severity level of dry mouth prior to any dosing. If the Challacombe score is 0, then the subject will not continue

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with study participation. If the Challacombe score is 1 or greater, subject will complete water-only evaluation.

4. Subjects will not be allowed to eat or drink during the study visit except for when directed by study staff.
5. Subjects will be asked to complete a Dry Mouth Inventory (DMI) questionnaire to understand their opinion on their severity of dry mouth prior to water evaluation.
6. Subjects will be asked to complete a Visual Analog Scale (VAS) for mouth dryness for a baseline mouth dryness score prior to water evaluation.
7. Subjects will drink 15 ml of water in their mouth and swallow the water.
8. Subjects will be asked to answer 1 question regarding mouth dryness at 5-, 15-, 30-, 60-, 120-, and 240-minutes post single dose, using a Visual Analog Scale (VAS) assessment format and a Product Performance Attribute Question (PPAQ) format of none/no relief, not enough, some/good, very good, significant/excellent.
9. Also, subjects will be asked to answer an additional PPAQ on the secondary endpoints at 5-, 15-, 30-, 60-, 120-, and 240-minutes post single dose using a format- poor, fair, good, very good, excellent.
10. Subject will be instructed on restrictions during the study (e.g., no spicy foods, medicine, oral care products, gum, hard candy).
11. Subject will be scheduled for Baseline Period 1 visit. Note: Subjects will continue with water only wash-in requirements and be randomized on treatment day.

Visit 3 - Baseline Period 1

1. Confirm that subject still meet the inclusion/exclusion criteria set forth in this protocol.
2. Confirm there were no changes to medications.
3. A study examiner will perform an oral exam and perform an assessment using the Challacombe-Scale to determine the severity level of dry mouth prior to any dosing.

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4. Photographs may be taken of the subject's mouth for publication and/or research development purposes, no diagnosis, treatment or decisions will be made from the photographs.
5. A salivary flow test will be performed to determine if there is any hyposalivation.
6. Subjects will be asked to complete a Visual Analog Scale (VAS) for mouth dryness for a baseline mouth dryness score prior to dosing.
7. Sealed envelope is opened, and treatment order noted.
8. Subjects will not be allowed to eat or drink during the study visit except for when directed by study staff.
9. Subjects will self-administer 1-2 sprays into their mouth using the first sample assigned based on the randomization card.
10. Subjects will be asked to answer 1 question regarding mouth dryness at 5-, 15-, 30-, 60-, 120-, and 240-minutes post single dose, using a Visual Analog Scale (VAS) assessment format and a PPAQ format of none/no relief, not enough, some/good, very good, significant/excellent.
11. Also, subjects will be asked to answer an additional PPAQ on the secondary endpoints at 5-, 15-, 30-, 60-, 120-, and 240-minutes post single dose using a format- poor, fair, good, very good, excellent.
12. The subjects will be given a subject diary and instructed to record frequency of use, number of sprays, and any side effects and/or adverse events they experience while using their assigned study product.
13. Subjects will be instructed to use the product at home for 7 days. They will be scheduled to return to the clinic with their product container and subject diary. They will present for their follow-up appointment without having taken any of their sample product.
14. Subject will be instructed on restrictions during the study regarding food, medicine, oral care products, gum, hard candy.
15. Subjects will be instructed to use the product at home at least 1X/day.
16. Subjects will be instructed to call the clinic if they experience any adverse events.

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17. Subject will be scheduled for a 1-hour appointment on the 7th day of Baseline Period 1 treatment.

Visit 4 - End of Treatment Period 1

1. Subjects will not be allowed to eat or drink during their study visit except when directed by study staff.
2. Confirm there were no changes to medications.
3. Photographs may be taken of the subject's mouth for publication and/or research development purposes. No diagnosis, treatment, or decisions will be made from the photographs.
4. A study examiner will perform an oral exam and perform an assessment using the Challacombe-Scale to determine the severity level of dry mouth.
5. Subject will be asked to complete questionnaire on product efficacy, usability and acceptability.
6. Subjects will return the sample bottle, to the research staff who will record its weight. They will also return their completed diary to the clinic research staff.
7. Subjects will be instructed on restrictions during the study regarding food, medicine, oral care products, gum, hard candy.
8. Subjects will be instructed about the wash-out period and told to use only the oral care products supplied by the study staff for at least a 2-day wash-out period. Additional study-supplied oral products may be distributed if needed.
9. Subjects will be scheduled to return in a minimum of 2-days for the period 2 treatment.

Visit 5-Baseline Period 2

1. Confirm subject completed the 2-day wash-out period.
2. Confirm there were no changes in medications.
3. Subjects will not be allowed to eat or drink during the scheduled study visit except when directed by study staff.

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4. Photographs may be taken of the subject's mouth for publication and/or research development purposes. No diagnosis, treatment or decisions will be made from the photographs.
5. Subjects will be asked to complete a Dry Mouth Inventory (DMI) questionnaire to document their opinion on their severity of dry mouth prior to any dosing.
6. Subjects will be asked to complete a Visual Analog Scale (VAS) for mouth dryness for a baseline mouth dryness score prior to any dosing.
7. A study examiner will perform an oral exam and perform an assessment using the Challacombe-Scale to determine the severity level of dry mouth prior to any dosing.
8. Subjects will be placed into their Period 2 treatment group.
9. Subjects will self-administer a 1 to 2 spray dose into their mouth of their assigned sample product.
10. Subjects will be asked to answer 1 question regarding mouth dryness at 5-, 15-, 30-, 60-, 120-, and 240-minutes post single dose, using a Visual Analog Scale (VAS) assessment format and a Product Performance Attribute Question (PPAQ) format of none/no relief, not enough, some/good, very good, significant/excellent.
11. Also, subjects will be asked to answer an additional PPAQ on the secondary endpoints at 5-, 15-, 30-, 60-, 120-, and 240-minutes post single dose using a format- poor, fair, good, very good, excellent.
12. The subjects will be given a subject diary to record frequency of use, number of sprays, and any side effects and/or adverse events.
13. Subjects will be instructed to use the product at home for 7 days and return to the clinic with the randomized sample and subject diaries on the 7th day prior to any doses of the randomized sample have been administered.
14. Subject will be instructed on restrictions during the study regarding food, medicine, oral care products, gum, hard candy.
15. Subjects will be instructed to use the product at home at least 1X/day.

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16. Subjects will be instructed to call the clinic if they experience any adverse events.
17. Subject will be scheduled for a 1-hour follow-up appointment on the 7th day of period 2 treatment.

Visit 6-End of Treatment Period 2

1. Subjects will not be allowed to eat or drink during the study visit except for when directed by study staff.
2. Confirm there were no changes to medication.
3. Photographs may be taken of the subject's mouth for publication and/or research development purposes, no diagnosis, treatment or decisions will be made from the photographs.
4. A study examiner will perform an oral exam and perform an assessment using the Challacombe-Scale to determine the severity level of dry mouth.
5. Subjects will return the sample bottle, to the research staff who will record its weight. They will also return their completed diary to the clinic research staff.
6. Subject will be asked to complete various questionnaire regarding product efficacy, usability, acceptability and preference. After these questionnaires are completed the subject has completed the study.
7. No further follow-up will be required, unless an adverse event occurred. In the case of an AE, the subject should continue to be followed until the AE has resolved.

See Appendix A for a table that summarizes the protocol procedures that will be performed at screening and for treatment.

5.2 Medication(s)/Treatment(s) Permitted

Subjects will not be permitted to take new or change the dosing of medications at the time of randomization that will change their dry mouth conditions during the study. Otherwise, there will be no medication or treatment restrictions for the duration of the study. Subjects will be expected to only use dry mouth oral care relief and oral hygiene study products provided. In general, subjects will not be permitted to use non-study products that affect, exacerbate or alleviate their dry mouth symptoms other than the study products provided.

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6. Assessment of Efficacy

6.1 Efficacy Parameters

- Primary endpoint
 - Mouth dryness
- Secondary endpoints
 - Feels comfortable in the mouth
 - Effectively lubricates the mouth
 - Soothing to the mouth
 - Effectively moistens the mouth
- Acceptance questionnaire
 - Likeability of flavor and mouth feel
 - Helps with eating, chewing, swallowing and speech difficulties
 - Fights malodor
 - Helps freshen breath
 - Improves my quality of life
- Usability questionnaire

6.2 Assessment Methods

Oral Tissue Exam

An oral tissue exam conducted by the study examiner will be completed at all visits to assess the soft palate, hard palate, oral mucosa, attached gingiva, tongue, sublingual and submandibular areas, salivary glands, tonsillar and pharyngeal areas, and teeth. Assessment responses will be given as Normal or Abnormal.

Salivary Flow Testing

Modified Schirmer tear strip Test (MST) - Testing with unstimulated saliva flow rate taken during the baseline period 1 visit (after wash-in and water only evaluation visits) to understand if the subject has hyposalivation and further characterize the study population.

This is an objective assessment where subjects are asked not to eat, drink, chew tobacco, chew gum, smoke, brush or floss teeth for 2 hours prior to Baseline Period 1 study visit. Test strips are placed on the floor of the mouth for 3-minutes to measure unstimulated flow rates. A calibrated paper that has an indicator that shows the amount of saliva present.^{5,6}

Challacombe Scale

The Challacombe Scale will be conducted prior to any dosing at all visits. Subjects with a score of 0 will not be enrolled in the study. Subjects with a score of 1 or greater, will be enrolled.

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This is an objective assessment to stratifying subjects into 3 groups representing their severity of dry mouth symptoms. A study examiner will conduct an oral exam and evaluate 10 symptoms. This scale works as an additive score of 1 to 10: 1 being the least and 10 being the most severe. Each symptom that is present is given a score of 1.

The Challacombe Scale of clinical oral dryness helps clinicians visually identify and quantify whether a patient has xerostomia. The 10 clinical signs are additive to determine severity.

✓	Dental mirror sticks to the patient's tongue	Total score helps you determine patient's level of dry mouth: ✓ Score of 1-3 = Mild ✓ Score of 4-6 = Moderate ✓ Score of 7-10 = Severe
✓	Dental mirror sticks to the buccal mucosa	
✓	No saliva pooling in the floor of the patient's mouth	
✓	Saliva is frothy	
✓	Patient's tongue shows generalized shortened papillae	
✓	Altered gingival architecture (i.e., smooth)	
✓	Patient's oral mucosa, especially the palate, appears glassy	
✓	Tongue lobulated/fissured	
✓	Patient has cervical caries on more than 2 teeth	
✓	Debris sticks to teeth or palate	

<http://www.challacombescale.co.uk/Challacombe-Scale-ENG.pdf>

Dry Mouth Inventory

Dry Mouth Inventory (DMI) will be conducted for each sample at the Water Only Evaluation visit and the Baseline Period 2 visit prior to any dosing.

This assessment is to understand the subject's opinion on their severity of dry mouth. Subjects will be asked to respond to 4 symptoms of dry mouth:

1. No moisture in the mouth
2. Lips sticking to the teeth
3. Tongue sticking to the roof of mouth
4. Throat dryness

This is an accumulative total score on a 6-point scale: Disagree (0), Disagree a little (0), Strongly Disagree (0), Agree a little (1), Agree (2), Strongly Agree (3).

Primary endpoint

The primary endpoint is relief of dry mouth, it will be scored using the Visual Analog Scale (VAS) – 10 cm long where the subject will score their mouth dryness. The anchor points of the scale are 0 represents “normal” (i.e., no dry mouth symptoms), and 10 representing “the worst imaginable” dry mouth symptoms.

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Use the VAS prior to dosing at the Water Only Evaluation visit and all remaining visits.

The primary endpoint of relief of dry mouth, post dosing, will also be evaluated by using a 5-point ordinal scale where none/(no relief) (1), not enough (2), some/good (3), very good (4), significant/excellent (5) are used.

This will be used after dosing on the Water Only Evaluation visit and Baseline 1 & 2 visits.

Secondary endpoints

Secondary endpoints will be scored using a 5-point ordinal scale where Poor (1), Fair (2), Good (3), Very Good (4) and Excellent (5) are used. Secondary endpoints are the formulation: feel comfortable in the mouth, effectively lubricates the mouth, soothing to the mouth and effectively moistens the mouth.

Use the 5-point ordinal scale to assess each sample at the Water Only Evaluation and sample evaluation visits after 1 dose at 5-minutes, 30-minutes, 60-minutes, 120-minutes, 240-minutes.

Also used to assess secondary endpoints will be the Visual Analog Scale (VAS) – 10 cm long where the subject will score their mouth dryness. The anchor points of the scale are 0 represents “normal” (ie, no dry mouth symptoms), and 10 representing “the worst imaginable” dry mouth symptoms

It will be used at the Water Only Evaluation and Baseline 1 & 2 visits, after 1 dose at 5-, 30-, 60-, 120-, 240-minutes.

Weigh bottles

Weights taken prior to any dosing at Baseline, Period 1 and 2, and after dosing at the End of Treatment for both Period 1 and Period 2 visits.

Subject Diary

To record subject's product use, any side effects, and adverse events if applicable.

Product Usability Questionnaires

This questionnaire will be completed for each sample at End of Treatment Period 1 and End of Treatment Period 2 visits.

Product Acceptability Questionnaires

This questionnaire will be completed for each sample at End of Treatment Period 1 and End of Treatment Period 2 visits.

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For description of analysis see section 8.2.1.

7. Assessment of Safety

7.1 Safety Parameters

The principal measures of safety will be the incidence of adverse events reported during the study.

Only treatment-emergent adverse event will be reported.

Examples of anticipated adverse events are:

- Temporary and mild, mouth or tongue sensations such as:
 - Numbness
 - Burning sensation
 - Tingling sensations
 - Taste alteration
- Superficial tissue sloughing on the inner surface of the cheeks, which is transient and painless.

7.2 Adverse Events

The Investigator is responsible for identifying adverse events that occur to each subject throughout the study and follow-up period. An adverse event can occur at any time during the conduct of the study, in any phase of the study or after the study is completed. An adverse event can be identified by the Investigator or reported by the subject.

Note: The Federal Privacy Rule (HIPAA) specifically permits the use and disclosure of protected health information “without written authorization of the individual” when used for public health activities such as reporting adverse events, tracking FDA-related products, enabling recalls, repairs, replacements, lookbacks, or conducting post-market surveillance [45 CFR 164.512]. This use and disclosure is subject to the *minimum necessary* standard, i.e. “the minimum necessary to accomplish the intended use, disclosure, or request” [45 CFR 164.502(b)(1)].

Definitions

- Adverse event (AE) means any undesirable clinical occurrence in a subject whether or not it is considered to be device or drug related.
- Device-related adverse event (i.e., adverse device effect) is an AE considered by the Investigator to have a reasonable likelihood of being associated with the experimental device.

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Serious adverse event is an adverse event or suspected adverse reaction which, in the view of either the investigator or sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- Serious adverse device effect is a device effect that has a serious adverse effect on health or safety causing hospitalization or prolonged hospitalization, or is life threatening or causes death.
- Unanticipated adverse device effect is any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to rights, safety and welfare of subjects.

7.3 Recording and Reporting

The Investigator records each material-related adverse event on an Adverse Device Effect Record. Documentation includes the description, severity, seriousness, date of onset and resolution, relationship to the experimental material, action taken and outcome.

The Investigator must promptly report an adverse device effect to the 3M Clinical Research Associate. If the adverse device effect is also considered by the Investigator to be serious and/or unanticipated, the Investigator must report it to the IRB as soon as possible and within IRB requirements.

A serious AE involving a non-3M commercialized product is reported to the 3M study monitor and IRB.

If a subject has no adverse device effect during the study, the absence of such must be recorded on the CRF.

8. Statistics

8.1 Data Sets Analyzed

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The intent-to-treat (ITT) data set will be the primary efficacy data set and will include all subjects randomized in the study. Subjects will be analyzed in the group to which they were randomly assigned. Subjects with missing post-baseline VAS scores will be included in the ITT analysis using appropriate input data sets and multiple imputation method.

A second per-protocol (PP) data set will be defined excluding any subjects with major deviations or lack of compliance with taking their treatments.

The major protocol deviations that will lead to exclusion from the per protocol data set include subjects missing the primary endpoint for one or both treatment periods, subjects not taking product for ≥ 2 days, and subjects taking excluded dry mouth products.

Deviations not captured above that will result in exclusion from the PP analysis will be defined and justified in a blinded fashion. In addition, documentation will be made of these data classification decisions prior to data lock.

8.2 Statistical Methods

The primary endpoint will be the paired-difference in VAS scores between experimental and active control product after 15 minutes of the first dose on the first day of the treatment period.

8.2.1 Efficacy Analyses

Primary efficacy analysis will be a mixed effects model of the VAS scores with baseline VAS (prior to first dose) included as a covariate and treatment group, period, and order assigned as fixed effects in the model. In addition, subject (group) will be included as a random effect in the cross-over model.

If the upper 95% confidence limit of the difference in VAS scores (experimental-control) is ≤ 1.5 then non-inferiority of the experimental product relative to the control product will be declared. Simultaneous testing of non-inferiority and superiority will be carried out without inflation of alpha error, maintaining a one-sided 0.025 significance level.

Secondary efficacy analyses:

To control the type 1 error rate, a fixed sequence of non-inferiority/superiority testing of the VAS dry mouth score differences will be conducted in the following order if the primary analysis at 15-minutes post first dose shows Treatment A is non-inferior/superior to the control Treatment B:

VAS dry mouth efficacy results immediately after use (within 5 minutes)

VAS dry mouth efficacy results 30 minutes after use

VAS dry mouth efficacy results 60 minutes after use

VAS dry mouth efficacy results 120 minutes after use

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VAS dry mouth efficacy results 240 minutes after use at baseline or at start of treatment period (after first sample dose)

A comparison of Treatment A against water will be carried out using a mixed effects model. The model of the VAS scores will have the baseline VAS (prior to first dose) and treatment group as fixed effects, and subject (group) will be included as a random effect in the model.

The responses on dry mouth relief, lubricating effects, soothing effects, comforting effects, and moistening effect, will be analyzed using a signed rank test for each of the two treatment arms at each time point. P-values will be adjusted using the Holm method for repeat testing done over time (5, 30, 60, 120 and 240 minutes) for families of hypotheses

Area under the curve (AUC) will be computed for the VAS endpoint and will be analyzed using an ANOVA model with baseline values, treatment group, order (or sequence) and period as fixed effects, and subject (group) as the random effect.

8.2.2 Safety Analyses

All adverse events (AEs) occurring after initiation of study treatment (treatment emergent AEs) will be summarized by severity, relatedness, overall and treatment group. AEs occurring during the screening period will be summarized separately. All AEs will be classified using the MedDRA dictionary.

All verbatim descriptions will be listed for all AEs, along with information regarding onset, duration, severity, relationship to treatment, and action taken.

Serious adverse events will be summarized and presented according to nature, time to onset, duration, relationship to treatment and outcome.

Fisher's Exact tests will be carried out to compare each preferred term between treatment groups. Testing will be carried out at a two-sided alpha level of 0.05.

8.3 Sample Size Justification

When the sample size in each group is 33, a paired t-test with a one-sided significance level of 0.01 will have 90% power to reject the null hypothesis that the test is inferior to the standard in favor of the alternative hypothesis that the treatment is non-inferior when the expected mean difference is 0.5, assuming that the non-inferiority margin is 1.5 and the standard deviation of the differences is 1.5. The sample size goal is inflated to 40 to allow for an approximately 15% drop out rate.

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References: Mouly et al. Drugs Aging 2007; 24(11) and Mouly et al Journal of Clin Psychopharmacology; 27(5) 2007. The former reference documented that the mouth dryness VAS responses at baseline and Day 14 end of study varied with standard deviations of 1.5, which is the basis for the non-inferiority margin of 1.5 chosen. In addition, standard deviations of VAS differences were 0.4 in the latter reference.

8.4 Interim Analyses Planned and Criteria for the Termination of the Study
There are no interim analyses planned for this study.

8.5 Procedures for Accounting for Missing, Unused, and Spurious Data
Missing efficacy data will not be imputed. Subjects lost to follow-up or discontinued will not be replaced.

8.6 Deviations to Statistical Plan
Any deviation from the original statistical plan will be described and justified in the final report.

9. Monitoring

3M, as sponsor of this study, is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the CRFs. 3M Company uses a risk-based approach to study monitoring. Protocol compliance and source data review will be conducted periodically (e.g., at a minimum of annually) by the assigned CRA. The progress of the study will be monitored by:

- Periodic on-site review
- Review of CRFs and source documents (e.g., patient hospital records, clinical charts, progress/doctor's notes, oral exam results)
- Telephone and email communications as needed

The Investigator will give the 3M study monitor direct access to source documents that support data on the CRFs and make available such records to authorized 3M, quality assurance, IRB, and regulatory personnel for inspection and/or copying.

Note: The Federal Privacy rule (HIPAA) specifically permits the use and disclosure of protected health information "to a person subject to the jurisdiction of the Food and Drug Administration (FDA) [e.g., study sponsor] with respect to an FDA-related product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety, or effectiveness of such FDA-regulated product or activity" [45 CFR 164.512(b)(1)(iii)].

10. Quality Control and Quality Assurance

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3M is responsible for implementing and maintaining quality assurance and quality control systems through written standard operating procedures (SOPs) to ensure that this study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and regulations cited in Section 1.5 of this protocol. Study monitoring is carried out to accomplish this.

A qualified individual designated by 3M, to evaluate study conduct and compliance with the protocol, SOPs, GCP and regulatory requirements, will conduct an independent audit of study records. (see ICH GCP Guidance E6 Parts 5.1, 5.19)

11. Ethics

This study will be conducted in accordance with the principles that have their origin in the Declaration of Helsinki, 21 CFR 50 (Informed Consent) and 56 (IRBs).

The study will start only after approval of the protocol and consent form by the IRB. The approval letter or notice must contain the IRB name and identification number, meeting date, and sufficient information to identify the protocol and informed consent by name and number that were reviewed. 3M, prior to study initiation, must receive a copy of the IRB approval letter.

12. Data Handling and Record Keeping

12.1 Study Personnel

Prior to study initiation, the Investigator must provide 3M with a signed investigator agreement (Statement of Investigator). The agreement contains pertinent investigator information (e.g., qualifications, experience, etc.) as well as the Investigator's commitment to conduct the study according to the protocol and all applicable state and federal regulations.

12.2 Pre-Study Documentation Requirements

Prior to study initiation, the Investigator must provide 3M with the following documents:

- Signed Statement of Investigator
- Signed protocol including any amendments in place prior to study initiation
- Curriculum vitae for the Investigator and any co-investigators
- IRB approved consent form.
- HIPPA Authorization form
- IRB study approval letter

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- IRB name, location and chairperson
- Financial Disclosure documents per 21 CFR 54
- Signed research agreement

12.3 Completion of Case Report Forms

3M intends to use electronic data capture (eDC) software for this study. Sites will be trained on the eDC software prior to study enrollment. Each site will be provided with a manual, including instructions on how to complete the CRFs and how to make CRF corrections. Data may be recorded onto data collection sheets (provided by 3M) prior to data entry or may be entered directly into the eDC system. Once the forms are completed, the monitor will review the CRFs to assure accuracy and completeness. The Investigator must review and sign the CRFs for each subject in a timely fashion following completion.

12.4 Final Report

3M will prepare and submit a Sponsor Final Report to all reviewing IRBs within 6 months after study completion or termination [see 21 CFR 812.150 (b)(7)].

12.5 Records, Reports and Retention Requirements

The Investigator will maintain study records for a minimum of 2 years following completion of the study. Records that must be maintained by the Investigator include, but are not restricted to:

- Signed study protocol, amendments, deviations
- IRB approval of protocol, consent form, authorization form* waiver of consent and/or authorization and amendments to any of these documents
- Applications to the IRB
- Signed consent and authorization forms
- Case report forms
- Adverse event reports
- Correspondence relating to the study
- Sponsor Final Report

*Note: “IRBs are not required to review and approve Authorizations under the Privacy Rule. Likewise, IRBs are not required to approve stand-alone Authorizations (i.e. Authorizations that are not incorporated into the informed consent document)”. [Institutional Review Boards and the HIPAA Privacy Rule, NIH Publication Number 03-5428, August 2003.] However, IRBs may require approval of the Authorization form at their discretion.

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13. Appendices

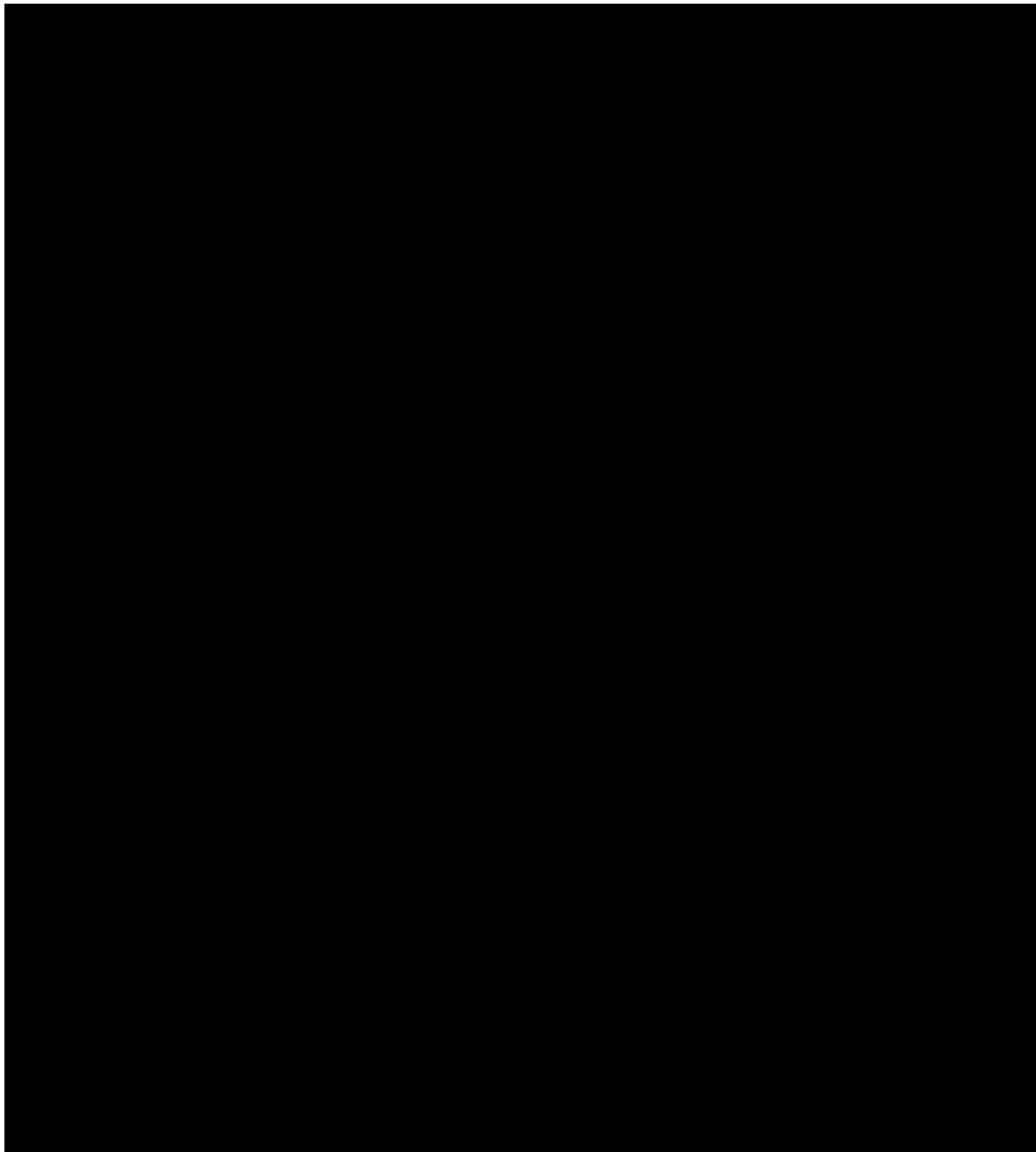
13.1 Appendix A - Study Schedule

Visit	Screening/Start of Wash-In	Water Only Evaluation	Baseline Period 1	End of Treatment Period 1	Baseline Period 2	End of Treatment Period 2
Subject Meets Inclusion/Exclusion Criteria	X	X	X			
Subject Consented	X					
Subject Authorization	X					
Health History and Changes to Concomitant Medication	X	X	X	X	X	X
Give directions for wash-in/out \geq 2-day period with water only	X			X		
Distribute oral care supplies (initially or as needed for on-going study)	X			X		
Subject Scheduled for Next Visit; give appropriate directions	X	X	X	X	X	
Subject Completed Wash-In \geq 2-day period with Water Only		X			X	
Study Examiner Completes Oral Tissue Exam/Challacombe Scale	X	X	X	X	X	X
Water Only Evaluation – subject swallows 15 ml of water		X				
Subjects Randomized			X			
Salivary Flow Testing			X			
Photographs Taken (Selective)			X	X	X	X
Subjects Complete Dry Mouth Inventory (DMI) prior to dosing		X			X	
Subjects Complete Visual Analog Scale for Mouth Dryness, prior to dosing		X	X	X	X	X
1-2 sprays of sample self -dosed by subject in clinic			X		X	
Subjects Completes Assessment for (post single dose): VAS Form PPAQ form Dry Mouth Relief		X	X		X	
Subject Diary and take-home sample distributed, along with review of directions for take home use			X		X	
Subject Diary Collected				X		X
Experimental Sample Spray Bottle Weighed			X		X	
Experimental Sample Spray Bottle Collected and Weighed				X		X
Adverse Events Assessed		X	X	X	X	X
Usability and Sample Acceptance Questionnaires				X		X
Preference Questionnaire, Study Discontinuation or Completion ¹						X

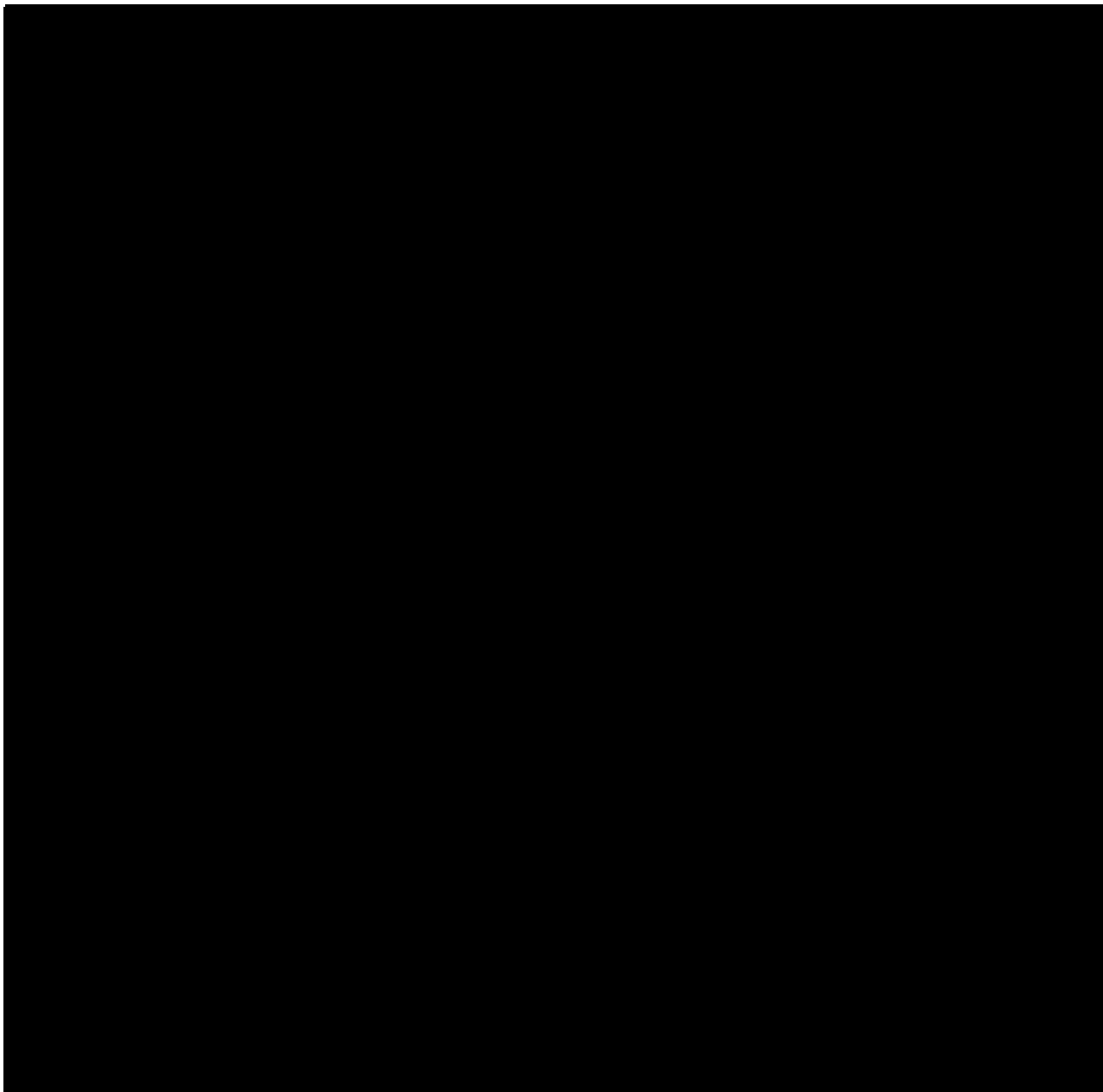
¹to be completed at the final visit or at any time the subject is prematurely discontinued

An unscheduled visit may occur at any time during the study that may require a spray bottle replacement, protocol deviation, adverse event, or oral examination forms to be filled out

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13.3 Appendix C – References

1. Anderson G, Johansson G, Attstrom R, et al. Comparison of the effect of the linseed extract Salinum and methyl cellulose preparation on the symptoms of dry mouth. *Gerodontology*. 1995;12:12-17.
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