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**DURATION OF EFFECT OF BIOTÈNE SPRAY
IN PATIENTS WITH SYMPTOMATIC DRY MOUTH**

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1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

To determine the duration of effect of a single dose of Biotène Moisturizing Mouth Spray in subjects who complain of a clinically dry mouth. The effect of the product will be compared to a control spray (water). A secondary objective is to assess how the perception of a dry mouth is related to the severity of actual hyposalivation.

1.2. Background

Xerostomia is a subjective feeling of a dry mouth which may or may not occur with decreased amounts of saliva in the mouth (Furness et al 2011, Sasportas et al. 2013, Jose et al. 2016). Complaints of xerostomia are typically related to resting discomfort and difficulty with functions such as eating and speaking. Xerostomia is commonly a permanent or temporary result of irradiation of salivary glands, autoimmune disease, smoking, alcohol use, and certain drug therapies. Regardless of the cause, the complaint of xerostomia warrants an evaluation for hyposalivation. Hyposalivation, which is a measurable decrease in saliva flow, is significant because of its destructive effects on oral tissues and reduced satisfaction with dentures. However, even when occurring in the absence of hyposalivation, complaints of xerostomia need to be addressed.

Currently, clinicians are recommending simple palliative therapies for xerostomia, which may include topical saliva substitutes, oral moisturizers, saliva stimulants in the forms of sprays, gels, gums, lozenges, mouth wash, and/or frequent sips of water. Recent reviews have weak evidence in favor of any particular topical therapy (Shahdad, 2005; Sasportas, 2013; Jose, 2016).

Biotène Moisturizing Mouth Spray is one such widely available over-the-counter (OTC) formulation which can be sprayed directly into the mouth for the relief of xerostomia. Although the spray is recommended empirically, its properties are not fully understood. One of the most important properties is its duration of effect in the mouth (Shahdad et al. 2005; Sasportas et al 2013). For example, how long a typical dose can be expected to last is not currently known. Manufacturers' instructions for the use of Biotène Moisturizing Mouth Spray state, "Spray directly into the mouth, onto the tongue, and spread thoroughly throughout the mouth. Use as required." For clinicians to effectively

advise patients and institutions (e.g. nursing homes), information about expected duration of effect is needed.

2. STUDY DESIGN

2.1. Overview

This double blind controlled randomized crossover study is designed to determine the duration of effect of a single dose of Biotène Moisturizing Mouth Spray. Because no detailed information about the duration of its effect is available now, a pilot study to determine sample size will be completed first. The spray consists of a mixture of starch, polymers, and plant oils which act as humectants to moisturize the oral tissues as well as flavorings that serve as salivary stimulants (Jose et al. 2016). Subjects complaining of a dry mouth will be recruited from the Division of General Dentistry of the Eastman Institute for Oral Health. Potential subjects will be scheduled for a screening appointment during which they will sign an informed consent form, complete a questionnaire about their experience with xerostomia, and then undergo a measurement of unstimulated whole saliva flow rate (UWSFR). Those whose UWSFR is \leq 0.2mL/min. will be admitted to the study and will then be administered a dose of either the experimental or control (water) agents. The unstimulated whole salivary flow rate of 0.2 mL/min is selected because it is widely recognized as the level at which actual mouth dryness occurs (Coulter et al, 2008). Statistical analysis will focus primarily on comparing the duration of action of the two agents but also collecting qualitative information about subjects' experiences with xerostomia and the two agents.

2.2. Rationale for Study Design

Xerostomia is a common oral health problem, with up to 50% of the population affected (Furness et al, 2011). A number of topical agents have been produced to help ameliorate the problem but evidence-based information about their indications and comparative effectiveness is sparse (Furness et al. 2011, Sasportas et al. 2013, Villa et al. 2015, Jose et al. 2016,). This study aims to compare the duration of effect of one widely available topical product (Biotène Moisturizing Mouth Spray) to water for the management of xerostomia. A pilot study is planned initially to determine the sample size for a definitive study. The double-blind design will avoid investigator bias after subjects are randomized to treatment groups.

2.3. Rationale for Dosage

The dosage selected for this investigation is three sprays (0.5 mL) from a primed metered-dose spray bottle identical to what is commercially available to patients. This dose was selected because we feel it simulates the dose a patient with xerostomia would

likely utilize. The spray will be administered by the investigator, Christine Lung, DDS, (CL) after priming the bottle twice prior to the providing the determined dose.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

Pilot Study

In order to establish adequate power at an acceptable level of significance for this study, an estimate of the duration of effect of the experimental and control is needed. At this time no such information is available; therefore a pilot study will be completed, as suggested by the study statistician (C. Feng, PhD). Results of the pilot will help determine the minimum number of subjects required for a definitive study. The following describes the characteristics of the population for the pilot study:

- a) **Number of subjects:** A total of 20 subjects enrolled is suggested by the biostatistician. A subject is considered in the total count once informed consent has been obtained and the inclusion criteria met. To account for dropout and disqualification of eligible subjects, 50 subjects will be recruited.
- b) **Gender and age of subjects:** Adults aged 18 years and over will be enrolled with no regard to gender, although it is recognized that xerostomia in the general population is more prevalent in older adults and in females (Fox et al. 1985).
- c) **Racial and ethnic origin:** Subjects will be recruited without regard to race or ethnicity.
- d) **Vulnerable subjects:** Vulnerable subjects (as defined by University of Rochester IRB Criteria) will not be enrolled.

3.2. Inclusion and Exclusion Criteria

- a) Inclusion Criteria:
 - Adults who are in good general health and reply initially affirmatively to the question, “Do you feel that your mouth is too dry and causes you discomfort at times during the day other than on awakening from sleep?” This question is an adaptation of the question used successfully by Jose and others (2016) to recruit study subjects.
 - Adults who are able to communicate easily in English and who are able to demonstrate understanding of the study instructions.
 - Adults who are physically able to perform an unstimulated whole saliva flow rate (UWSFR) test and who produce 0.2 mL/min or less of saliva.
- b) Exclusion Criteria:
 - Adults under the care of a health professional specifically for xerostomia treatment, including those taking prescription systemic parasympathetic medications.

- Adults who regularly “self-medicate” their xerostomia with water or other agents or products designed to treat their xerostomia and are unwilling or unable to cease use of the agent for at least 48 hours prior to the two test visits.
- Adults who are primarily mouth breathers (i.e. mouth breathing secondary to nasal obstruction)
- Adults who cannot consent for themselves or have physical/mental disabilities requiring a caregiver.
- Adults with a known allergy to any of the ingredients in Biotène Spray (eg. dairy allergy)

3.3. Discussion of the Subject Population

The inclusion criteria target the large proportion of the adult population (up to 50%) (Furness et al, 2011) who are generally healthy but complain of a dry mouth. This enrollment strategy focuses on a “real world” dry mouth population who might use these treatments for the daily management of their symptoms. The exclusion criteria are aimed to eliminate factors and conditions that might artificially limit typical saliva flow. Subjects who have unstimulated whole salivary flow rates above the 0.2 mL/min threshold will be excluded to reduce the variation among subjects and minimize the possible participation of those who are unable to discriminate between lower and higher flow rates; this latter group may be studied further in another investigation.

4. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

4.1. Method Of Subject Identification And Recruitment (See Appendices 1 and 2)

Subjects will be initially identified and recruited at all the dental clinics of the Eastman Institute for Oral Health (EIOH) at the University of Rochester, Rochester, NY, by the strategies described here. Those identified will be assured, from the outset, that neither their clinical care at EIOH nor their healthcare anywhere else in the University Medical Center will be affected by their decision whether or not to take part in the study.

1. Investigators’ patients. Both Drs. Lung and Saunders see EIOH patients regularly. They will recruit patients directly from their patient pools by advising them of the study and inclusion and exclusion criteria. They will pose the question regarding discomfort from xerostomia detailed in section 3.2 a) above to any adult patients who appear to meet the inclusion criteria; those who respond affirmatively will be identified as potential subjects. Definitive qualification will follow as the subjects complete the consent process and the UWSFR test.
2. Recruitment posters. Posters will be placed in hallways, near elevators, and within the dental operatories at the clinics and which will indicate that the study is underway. The posters will include the basic inclusion and exclusion criteria and the information that those who are interested should contact Dr. Christine Lung by phone

or e-mail; her contact information will be included (Appendix 3). Those who enter the study by this route will be considered to have “self-identified” themselves as potential study subjects.

3. Meetings with dental residents. Dr. Lung will meet with her fellow dental residents to explain the study, provide posters, and request their assistance in recruiting potential subjects from among their pool of regular patients.

Potential subjects will be asked to contact the investigator for a screening appointment at the study site and will be offered the consent form (please see next section 4.2 for details.), which includes details of the study to read and consider at their leisure and with others (e.g. family members, their personal dentists). They will be advised that, on completion of both sessions of the study, they will receive \$75 plus parking in appreciation for their time and effort. Persons who meet the inclusion criteria and sign the consent form will be considered recruited for the study.

As subjects qualify for the study, they will be placed, according to a randomization table (Appendix 4), in either one group (Group A) or the other (Group B). If a patient being recruited is found not to meet the inclusion criteria, s/he will be dismissed and the next potential candidate will be evaluated for admission to the study.

Patients will be assured that their regular clinical care will not be affected by their decision to participate or not participate in the study. Similarly, enrolled subjects who withdraw from the study will be assured that they will continue to receive their regular clinical care.

4.2. Process of Consent (Please see draft Consent Form) attached.)

After the initial discussion about the study, the investigator will provide the prospective subject with a paper consent form which describes the study in detail. The subject will be informed that they may undergo temporary discomfort during the study, and so this is a consideration whether or not to participate. As previously described, potential subjects will be given every opportunity to discuss or ask questions of the investigators that occur to them. They will be advised of any anticipated risks and contact information for the investigators and others affiliated with the University who could assist with any problems which might develop and personnel who might carry responsibility for subjects’ safety. The consent form will carry a statement to the effect that subjects may withdraw from the study at any time without affecting their eligibility for dental care or other care at the University and without any other penalty. The subject must give her/his own consent without a caregiver, spouse, or legal guardian. Signed consent forms will be paper documents stored in a locked file cabinet accessible only to the investigator on an electronically locked laboratory floor.

5. METHODS AND STUDY PROCEDURES

5.1.1. Treatment Dosage and Administration.

The methods and study procedures will consist of the following 11 parts which will be completed during a recruitment encounter and two testing visits. (See also Appendices 5 and 6).

Recruitment Encounter

This will be brief and will occur at the time the potential subject volunteers to be considered for the study. (Please see below for details.)

Visit 1

1. Sign consent form (if not completed at Recruitment Encounter.)
2. Update of medical history and recording of blood pressure and pulse.
3. Questionnaire about subject's xerostomia experience.
4. Determination of unstimulated whole saliva flow rate.

The inclusion criteria for the study require that the rate be ≤ 0.2 mL/min. A subject's participation will be terminated at this point if this inclusion criterion is not met.

5. Trial with randomly assigned alternative or experimental agent.
6. Post-test study questionnaire about study agent.

Session 1 is complete at this point. An appointment will now be scheduled for Session 2.

Washout Period

As is usual in studies utilizing a crossover design a "washout period" will be employed in this investigation. The retention time appears to be related to the viscosity of a topical agent for the relief of a dry mouth (Shahdad et al. 2005). Therefore, a washout period of at least 48 hours, to be utilized here, appears to be sufficient to eliminate the effects of a single application of Biotène.

Visit 2

1. Update of medical history and recording of blood pressure and pulse.
2. Determination of unstimulated whole saliva flow rate. Subjects will continue in the study regardless of their salivary flow rate at this point. The mean of the UWSFRs measured at Sessions 1 and 2 will be used in calculations comparing flow rates to duration of action of the two agents. This will be done as a matter of interest in the amount of variation that may exist between the 2 UWSFR measurements.
3. Trial with either control or experimental agent, whichever was not tested in Session 1.
4. Post-study questionnaire about study agent, whichever was not tested in Session 1.

Each of the two testing visits is expected to utilize as much as three (3) hours but may be less, depending mainly on subjects' responses to the test agents. Both sessions will be

scheduled in the time period 830am – 1230pm to control for known variations in daily flow rates.

Detailed descriptions of each part follow here.

Recruitment Encounter

This encounter would commonly occur during or after a routine clinic visit or otherwise after s/he learns of the study. At this time the investigator would read to the potential subject a scripted question plus a limited statement of eligibility. If the investigator continues to feel that the subject may be eligible s/he will be encouraged to sign the consent form. At the potential subject's request s/he may take the consent form for the purpose of further consideration personally or with family, other health professionals, etc. and return it at the first experimental visit. (See Appendix 1 for Scripted Recruitment Statement).

Visit 1

1. Sign consent form if this was not done at the Recruitment Encounter. Update of subject's medical history and measurement of vital signs (blood pressure, pulse, respiration rate, presence and level of any pain.).

2. As also indicated previously, when subjects are initially contacted about the study they will be given a consent form to take with them and consider participation, possibly including discussions with family, health professionals, etc., and then return to the investigator. If any questions exist the investigator will respond and then require that the consent be signed by both the investigator and subject prior to proceeding. A copy of the signed form will be given to the subject and the original retained by the investigator in a locked file in a University facility accessible only to investigators.

3. Survey of Experience with Xerostomia. (Appendix 7)
 A secondary aim of the study is to gather qualitative information about subjects' experiences with xerostomia. A tested 6-item written questionnaire will be administered at this time.(Shahdad et al, 2005) for this purpose. The time needed for completion of this brief questionnaire is estimated at 5 minutes.

4. Determination of Unstimulated Whole Saliva Flow Rate. (UWSFR) (See Appendix 8)
 The purpose of this test is to determine whether or not potential subjects have a rate of not more than 0.2 mL/min. The UWSFR test will be completed in a quiet room with lighting generally at a low level but bright enough to allow for reading. Subjects will be seated in a cushioned chair and encouraged to make themselves as relaxed and comfortable as possible. A pre-weighed plastic disposable drinking cup (+/- 0.01 g) will be given to the subject with instructions to cease the normal process of swallowing when

saliva accumulates but rather allow it to accumulate in the mouth and then drain gently into the cup. The time will be noted by the investigator and, after 15 minutes, the investigator will advise the subject that the test has ended. The investigator will again weigh the cup and saliva and record the weight. One gram will be understood to be approximately equivalent to 1 mL of saliva and the new weight recorded. The weight per minute will be calculated and understood to be the subject's current unstimulated whole saliva flow rate (UWSFR). If the rate is < 0.2 mL/min the subject will be advised that the inclusion criteria for the remainder of the study have been met and that the study will continue. This level was selected as a "cut-off" both because it is the level at which existing literature recognizes genuine mouth dryness to likely exist and also because of our belief that subjects who perceive dryness in the presence of relatively 'normal' salivary flow rates, may be unreliable in their reports of beneficial effects of study agents. Subjects who do not meet the inclusion criteria will be given \$25 in appreciation for their participation to this time and then dismissed.

6. First Test agent.

The subject will then be seated in a quiet dimly lit room and asked to refrain from speaking, including using phones, unless it is essential (e.g. they are feeling badly enough that their participation needs to be paused or stopped). After not less than one (1) minute a visual analog scale (VAS) of dryness will be recorded in response to the question, "How much discomfort are you feeling from your dry mouth?". (See Appendix 9). They will then be administered, by the investigator, a dose of 3 sprays (to the anterior dorsal of the tongue) of the randomly selected experimental or alternative agent with instructions to "spread it around in your mouth." An electronic timer will be started by the investigator at that time. The investigator will be administering the agents after priming the spray bottle twice before aiming the first spray to the anterior dorsal of the subject's tongue. Neither the investigator nor the subject will know the identity of the administered agent.

One minute after the spray a second VAS will be recorded. For every 15 minutes elapsed, the investigator will repeat the question, "How much discomfort are you feeling from your dry mouth?" Subjects' responses will be recorded each time. Subjects will be instructed to stop the timer when they feel that the effect of the administered agent has dissipated completely (Appendix 10).

Studies with other more viscous moisturizing agents have rarely found the duration of effect to be more than two (2) hours. Therefore, the maximum amount of time subjects in this study will be tested is two (2) hours (Jose et al, 2016). The endpoint for each subject, however, will occur the subject feels that the effect of the agent has dissipated; the

duration of effect will be the time between starting the timer and the elapsed time to the endpoint.

6. Survey of Experience with First Test Agent.

A secondary objective of this study is to gather new information about subjects' perceptions of the characteristics of agents designed to relieve xerostomia. However, a review of literature utilizing PubMed and references from other investigations did not reveal a standardized survey tool for this objective. Therefore a new post-test questionnaire about agents designed to ameliorate xerostomia was designed by investigators and will be administered (Appendix 11). This information could be useful in the subsequent full study to help determine whether or not further efforts are needed to mask any potentially noticeable differences between agents being tested. This is a 9-item survey of a variety of characteristics of potential agents. A printed copy of the survey attached to a clipboard and also a black-ink pen will be handed to the subject. The subject will be instructed to circle the best answers and then return. The use here of this questionnaire will constitute a pilot study because it is new and has not yet been validated.

At this time the subject will be given a check for \$25, an appointment for the second visit, and dismissed for the day.

Washout Period

A period of at least 48 hours will be required prior to Visit 2.

Visit 2

1. Update of medical history and recording of blood pressure and pulse.
2. Second sialometry to determine a second UWSFR.
3. Administration of second test agent (which ever was not used in Session 1). Recordings of VAS regarding the feeling of dryness will be made just before and after administration of the test agent and then every 15 minutes in a manner identical to that of Session 1. Subjects will be instructed to stop the timer when they feel the effect of the test agent has dissipated completely; this will mark the endpoint of the duration of effect, which will be recorded.
4. Survey of experience with second test agent.

This will utilize the same survey form used in Session 1 (Appendix 11).

At this point, the subject has completed the required commitment to the study, and will be de-briefed, including being requested to verbally supply any comments they feel might be useful in future studies in which they might participate. Subjects will be offered additional

information and/or referrals to a dry mouth clinic as needed. They will be compensated \$50 plus parking for their participation and dismissed.

(See also Appendices 4 and 5 for flow chart and schedule of activities.)

5.1.2. Amount of agent to be tested. And 5.1.3. Investigational drug/device.

The manufacturer of Biotène Moisturizing Mouth Spray has directions (Appendix 12) printed on the spray bottle stating, “Spray directly into the mouth, onto the tongue, and spread thoroughly inside the mouth. Use as required. Safe to swallow when used as directed.” In an effort to minimize variation in the amount dispensed for this study but to remain essentially consistent with the manufacturer’s directions the investigator will assume the following calibration protocol for each subject:

1. Weigh the empty cup to be used for collection of whole saliva.
2. Prime the spray bottle by squeezing firmly at least twice, toward a sink or bucket. This “spray sample” will then be discarded.
3. Using the identical technique, three sprays will then be collected in a second empty cup and weighed. This will serve as a “calibration sample.” This sample will then be discarded but the empty cup retained.
4. The investigator will then direct three sprays to the anterior dorsal of the tongue. Utilizing a total of three sprays is intended to mimic what a xerostomic patient likely would do. Having the investigator, instead of the subject, administer the agent is expected to make the amount of agent expressed be generally uniform among subjects.
5. The same cup will be handed to the subject and will be used for collection of the sample of whole saliva over a period of 15 minutes.

The organization and administration of the test agents will be completed in the laboratory of Stephen A. Bean, Pharm D, Manager of Investigational Drug Services (IDS) here at the University. Each bottle of test agent (either Biotène Dry Mouth Moisturizing Spray or sterile water) will be appear in identical spray bottles. The possibility exists that the investigator or subject may notice the scent and viscosity differences between the different agents, however this will unlikely impact the outcome measures. To assess the impact of these differences, the post-test questionnaire (Appendix 11) will ask subjects if they think they received the moisturizing spray or the alternative (sterile water). The spray bottles will be unlabelled except for a unique number which identifies the contents to IDS laboratory and the statistician. The true identities of the bottles will be unknown to the investigator and the subjects. The contents of the test agent will be linked to each subject through a randomization process completed by IDS.

A recent study (Jose et al, 2016) sponsored by the manufacturer (GlaxoSmithKine) of Biotène spray investigated the comparative effect of 3 of its products with 2 hours as the primary endpoint. Since xerostomia lasting longer than 2 hours may be uncomfortable, demonstrating that an agent provides relief close to this time frame would have potential therapeutic and commercial value. Although the study design was different, 49.5% of subjects reported that the spray was good, very good, or excellent at “relieving the discomfort of dry mouth” 2 hours after use of the spray. A previous study (Shahdad et al. 2005) also discovered that most subjects achieved relief utilizing topical agents after 2 hours. In this study involving a Biotène gel, it was found that the viscosity is positively correlated to the retention time of the agent (Shahdad et al. 2005). Therefore, we expect the less viscous experimental spray to have a shorter retention time than the expected 2 hours. Therefore, 2 hours will be defined as the maximal endpoint in this study. We expect that the crossover design and qualitative measures will aid health care providers and patients to derive benefit from Biotène Moisturizing Mouth Spray or water.

This crossover study will employ a washout period of 48 or more hours. The dose being administered to a subject is small, and the retention time is related to the viscosity of a topical agent for the relief of a dry mouth (Shahdad et al. 2005). Therefore, a washout period of at least 48 hours appears to be sufficient to eliminate the effects of a single application of Biotène.

5.2. Efficacy Assessment

This pilot study was developed because estimated data regarding the duration of action of a single dose of Biotène Moisturizing Mouth Spray is not available. The estimated duration is necessary for calculating the sample size for a definitive study. At the completion of the pilot, the mean duration of action of both the experimental and control agents will be forwarded to the biostatistician (Changyong Feng, PhD) for calculation of the sample size for the definitive study. When the required sample size is returned to investigators, plans for the definitive efficacy assessment will be developed.

5.3 Safety Assessments

During subject identification and recruitment comprehensive medical histories of potential subjects will be gathered. Persons whose histories suggest they are rated ASA III or higher will not be accepted in the study. At the beginning of each visit subjects’ medical histories will be updated and their vital signs (blood pressure, pulse, respiration rate, presence and level of pain) will be recorded by the investigator. If the investigator, who is a dentist, feels that the subject would not be a safe candidate for a routine dental procedure that day, s/he will be re-scheduled to another day or discharged from the study.

5.4. Assessment of Subject Compliance

Subjects will be under the direct supervision of the investigator during the observation period for up to 3 hours.

5.5 Data and Speciman Banking for Future Research Use

N/A

5.6 Genetic/Genomic Research Activities

N/A

5.7 Costs to the Subject

There are no costs for subjects nor for potential subjects.

5.8 Payment for Participation

Potential subjects who are screened for the study will be compensated for parking in the ramp garage plus \$25 for their first session. Eligible subjects who return and complete the second session will be compensated for their parking plus an additional \$50.

5.9 Return of Individual Research Results

In their second session subjects will be offered the results of their sialometry flow test and an interpretation by the investigator. At their request, patients who have concerns about their test results will be given additional general information about managing their condition and also encouraged to see their own dentist or the EIOH Oral Medicine Clinic for further evaluation.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Subjects may take normal daily medications as usual.

7. SUBJECT WITHDRAWALS

Eligible subjects will be enrolled into the study on a rolling basis until a minimum number of subjects is attained. If the withdrawal of a subject causes an insufficient number of subjects to be enrolled, the recruitment of another subject will be undertaken.

8. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

Note: The side of the box with the device information is included in Section 50 of the RSRB application.

8.1. Biotène Dry Mouth Moisturizing Spray

Biotène Dry Mouth Moisturizing Spray (Appendix 12) contains water, polyglycol, propylene glycol, sunflower oil, xylitol, milk protein extract, potassium sorbate, acesulfame

K, potassium thiocyanate, lysozyme, lactoferrin, lactoperoxidase (45 mL). No maximum dosage or interval for usage is specified. Product is to be used *ad libitum*. The Investigational Drug Lab at the University of Rochester Strong Hospital, 601 Elmwood Ave, Rochester, NY will be supplying, packaging, and labeling the product as well as the placebo which will consist of distilled water.

The agent of interest is IND/IDE exempt for this clinical investigation as the product is lawfully marketed in the United States for the treatment of symptoms of dry mouth [FDA 21 CFR 312.2(b)/FDA 21 CFR 812.2(c)].

8.2.Dosage of Study Drug/Biologic

For the purpose of this study, 3 streams of the product (approximately 0.5 mL) administered by the investigator will be considered a dose. For consistent dosing, two sprays to prime the spray nozzle will be completed prior to administering a dose to the subject.

8.3.Subject Enrollment/Randomization

Subjects will be allocated to group A or group B using block randomization (Appendix 6). Subjects will be allocated to a group as they qualify for the study. The subject and the investigator will be blinded to the group a subject is allocated to. The products will be labeled identically except for a serial code on the bottle will correspond to the treatment or control. The true identity of the products will be known only to the supplier (the Investigational Drug Lab, University of Rochester Strong Memorial Hospital), and unknown to the investigator and subjects until the completion of the study.

8.4.Accountability of Investigational Supplies

The Investigational Drug Lab of the University of Rochester Strong Memorial Hospital, 601 Elmwood Avenue, Rochester, NY will be responsible for the formulation and labeling of investigational supplies. The Investigational Drug Lab will be the unblinded third party. The investigator will handle the receipt, storage, dispensing, collection, accountability log, and disposal of the investigational supplies.

8.5.Subject Withdrawal of Study Drug

The agents under investigation have short-lasting and reversible effects that do not require the subject to be monitored following the study period. Subjects may choose to withdraw from the study at any time without consequence and without side effects. The effect of the agents under investigation can be reversed by rinsing out the mouth with warm water.

8.6.Emergency Drug Disclosure

Drug disclosure will be maintained electronically and in envelopes by the Investigational Drug Lab. Drug disclosure should be accessed only in the case of a medical emergency. If

such action is necessary, the Investigational Drug Lab will provide the identity of the administered agent to the investigator and the appropriate medical team will be called. Once the identity of the administered agent is revealed, the subject will be withdrawn from the entire study.

9. SAFETY AND REPORTABLE EVENTS

9.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

9.2. Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

9.3. Recording Adverse Events

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. After the study visit, the subject should be questioned directly regarding the occurrence of any adverse experience during his/her visit.

All adverse events, whether observed by the investigator, elicited from or volunteered by the subject, will be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., agent or control), contributing factors, and any action taken with respect to the study agent.

The timeframe that recording of adverse events will occur once the subject signs consent until subject completes the study or withdraws from participation. Follow up will occur until the adverse effect has resolved. Follow up of adverse experiences after the subject concludes study participation should be with the investigator, who may decide to refer the subject to a primary care physician.

9.4. Responsibilities for Reporting Serious Adverse Events

The Investigator will record all serious adverse experiences that occur during the study period in the appropriate source documents and/or adverse event (AE) log as applicable. The study period for reporting serious adverse events is from the time of signing consent to the end of the study participation. The principal investigator and appropriate medical response teams will be notified immediately. The Investigator will comply with regulations and RSRB policy regarding the reporting of adverse events.

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks

As with all studies, there is a risk of breach of confidentiality. Subjects may be exposed to substances that may elicit an allergic reaction. Also, subjects may undergo temporary oral discomfort while their usual methods of moistening their mouths are forgone.

10.2. Protection Against Risks

The study design minimizes risk by administering a single dose of the agents being tested. The subjects in the study will be under constant surveillance by the investigator. The investigator has a Basic Life Support Training. Follow up of subjects who experience an adverse effect will be followed up by the investigator at no charge, otherwise referred to a primary care physician at the subject's expense.

10.3. Potential Benefits to Subjects

There are no benefits to participating in the study.

10.4. Alternatives to Participation

There is no alternative to participating in the study.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Confidentiality is the ethical and/or legal right that information, such as research data, will be held secret and safeguarded from disclosure unless consent is provided permitting disclosure. The subject data will be identified in the research data set using a unique random sequence of numbers. The random unique code along with all data sets related to the study will be maintained by the investigator and will be destroyed 36 months following the completion of data analysis.

The research data will be stored on a password protected file on an encrypted flash drive using a subject ID number. The flash drive will be stored in a cabinet in a locked office accessible only to the investigator. Transfer of research data will only occur on a computer between flash drives. Transfer of research data will not be done through email, cloud storage, or FTP or secure FTP.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

Results of sialometry flow test will be recorded in the subject's dental chart.

13. DATA ANALYSIS AND MONITORING

13.1. Sample Size Determination

Because estimated durations of the test agents are not available, this pilot study is being undertaken. The number of subjects needed for this pilot study is 20, as recommended by the biostatistician.

13.2. Planned Statistical Analysis

After completion of the pilot study the number of subjects necessary for the definitive study will be calculated by the biostatistician.

13.3. Data and Safety Monitoring

Data and safety monitoring by the principal investigator is appropriate because the study is considered minimal risk and will be conducted at a single site. Prompt reporting of reportable events and other study-related safety information will be made to the RSRB and sponsor.

14. REFERENCES

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3. Furness S, Worthington H, Bryan G, et al. Interventions for the management of dry mouth: topical therapies. Cochrane Database System Reviews. 2011. www.ncbi.nlm.gov/pubmed/22161442.
4. Jose A, Siddiqi M, Cronin M, DiLauro TS, & Bosma ML. A randomized clinical trial in subjects with dry mouth evaluating subjective perceptions of an experimental oral gel, an oral rinse and a mouth spray compared to water. American Journal of Dentistry 2016; 29 :58-64.
5. Sasportas LS, Hosford DN, Sodini MA, Waters DJ, Zambricki EA, Barral JK, et al. Cost-effectiveness landscape analysis of treatments addressing xerostomia in patients receiving head and neck radiation therapy. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 2013; 116: 37-51.
6. Shahdad S, Taylor C, Barclay S, et al. A double-blind study of Biotene Oralbalance and BioXtra systems as salivary substitutes in patients with post-radiotherapy xerostomia. European J Cancer Care. 2005: 15: 319-26.

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8. Villa A, Connell CL, & Abati S. Diagnosis and management of xerostomia and hyposalivation. *Therapeutics and Clinical Risk Management* 2014;11:45-51.

Appendix 1 – Example script for screening subjects at the recruitment encounter

Investigator:

Hello, I understand you have heard of our study and may be interested in participating. Are you age 18 or older?

Potential subject:

Yes No

Investigator: (If “yes”):

Do you frequently have the feeling of dryness of your mouth that gives you discomfort at times of the day in addition to when you first wake from sleep?

Potential subject:

Yes No

Investigator: (If “yes”):

Do you regularly (at least daily) use any type of medication or product other than water to help relieve the feeling of dryness?

Potential subject:

Yes No

Investigator: (If “no”):

Proceed to next question

Investigator: (If “yes”)

Would you be willing and able to cease using the product for at least 48 hours (2 days) before each of the two test visits required by the study?

Investigator: (If “No”)

I’m sorry then you would not be a candidate for this study. Thank you anyway.

Investigator: (If “Yes”)

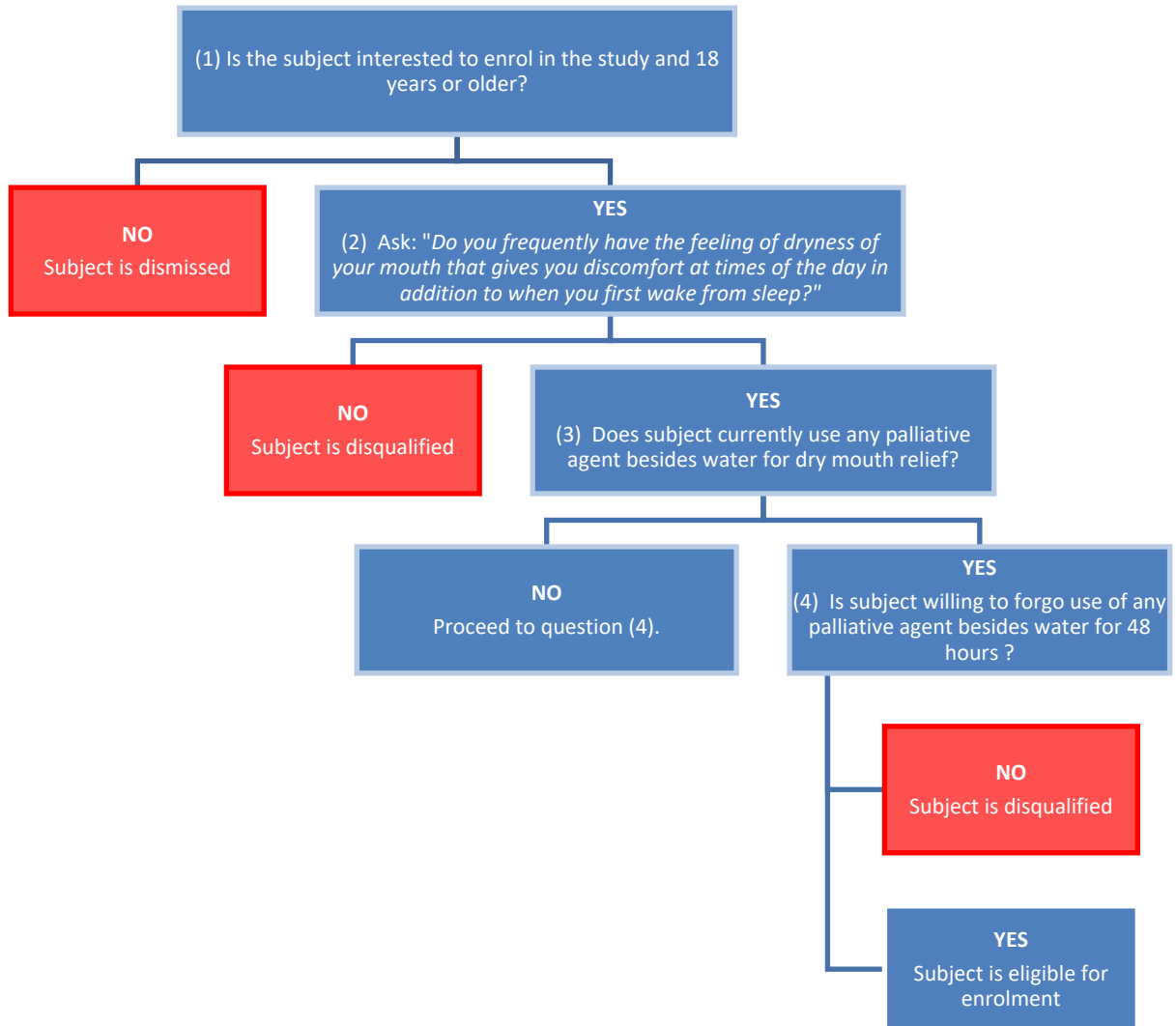
If Yes

Fine, then let’s look for an appointment for your first test visit. Please know, however, that at this first visit, we must perform a test of your saliva for which you will be given \$25 plus the cost of your parking. If the results show a certain result, we will want you to return for a second and final visit. If not, we must dismiss you from the study at that time.

If, however, we find that we do have the result required by the study, we will then schedule an appointment for the final visit, for which you will receive a payment of \$50 plus the cost of your parking.

Do you have any questions?

Thank you for your interest in our study.

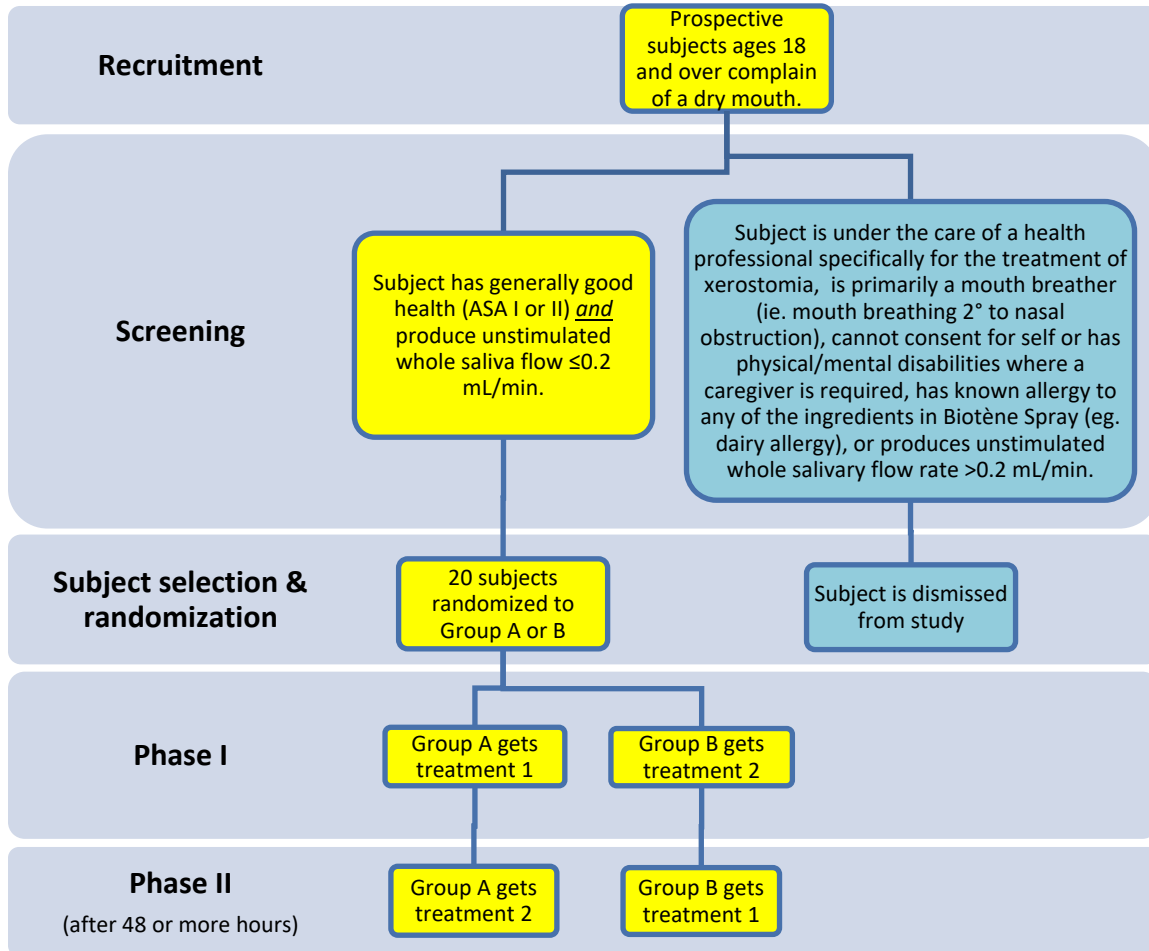
Appendix 2 – Flow diagram for screening subjects at the recruitment encounter

Appendix 4 – Six Block Randomization Table

At enrollment, subjects will be randomly allocated to a number from 1-6 using the random blocks shown above. The true identity of the products (Biotène or distilled water) will be known only to Investigational Drug Services, University of Rochester Strong Memorial Hospital.

523164	123465	521364	241563	435162	214653
254163	345612	251634	246153	164325	436512
561234	134562	615342	432561	546132	642413

Appendix 5 – Flow diagram for subject recruitment, selection, and study design



Appendix 6 – Checklist for study procedures to be performed

Schedule of Activities

Session	1	2
Obtain informed consent.	X	
Confirm eligibility/enroll.	X	X
Medical history and vital signs.	X	X
Sialometry test	X	X
Test 1 (Biotene or Water)	X	
Post-test Survey of First Product	X	

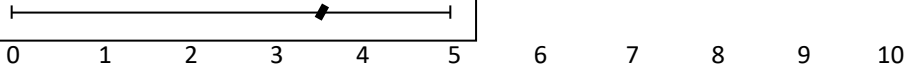
Medical history and vital signs.		X
Test 2 (Biotene or Water)		X
Post-test Survey of Second Product		X
Post-test survey of xerostomia experience.		X

Appendix 7 - Patient Xerostomia Experience and Severity Questionnaire
Continuous variables recorded on a visual analogue scales (VAS)

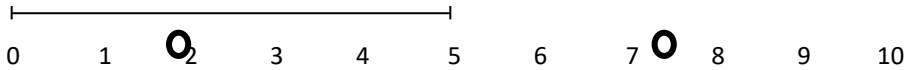
Chart number: _____ Subject's Initials: _____ Date: ___/___/___

Please respond to the following questions by *placing a single mark on the line*.
 The numbers below the scale are references only.

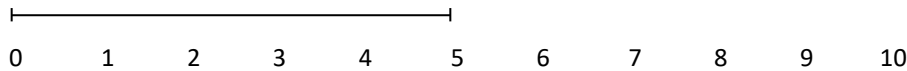
Acceptable:



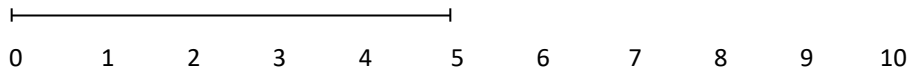
Not acceptable:



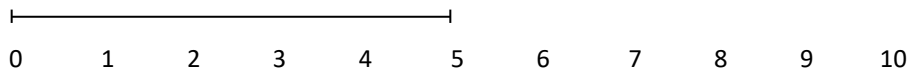
1. How dry is your mouth? (Extremes: 0 = 'not dry at all', 10 = 'worst imaginable dryness')



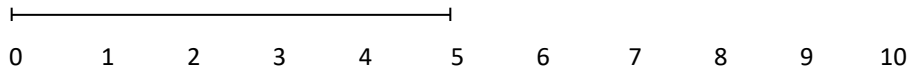
2. Do you have difficulty chewing because of your dry mouth? (Extremes: 0 = 'no difficulties at all', 10 = 'very severe difficulties chewing')



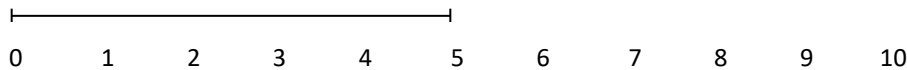
3. Do you have difficulty swallowing because of your dry mouth? (Extremes: 0 = 'no difficulties at all', 10 = 'very severe difficulties swallowing')



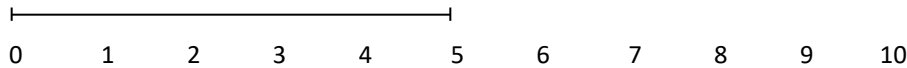
4. Is speech difficult because of your dry mouth? (Extremes: 0 = 'no difficulties at all', 10 = 'very severe difficulties with speech')



5. Is taste affected by your dry mouth? (Extremes: 0 = 'not affected at all', 10 = 'very severe alteration of taste')



6. Do you have a burning sensation in your mouth? (Extremes: 0 = 'no burning at all', 10 = 'very severe burning mouth')



**Appendix 8 – Sample data collection form for unstimulated whole saliva flow rates
(mL/min)**

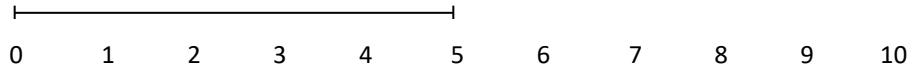
Subject ID	Date	Subject Age	A -Wt of collected saliva (mg)	UWSFR 1 (A / 15 min)*	Date	B -Wt of collected saliva (mg)	UWSFR 2 (B/ 15 min)*
174							
938							
235							

* Calculation based on specific gravity 1 mg = 1 mL

Appendix 9 - Level of discomfort a patient is feeling on a visual analog scale.

Chart number: _____ **Subject's Initials:** _____ **Date:** ___/___/___

How much discomfort are you feeling from your dry mouth? (Extremes: 0 = 'no discomfort', 100 = 'worst imaginable discomfort/dryness')



Appendix 10 – Sample data collection form for endpoint and VAS scores.

Subject ID	VAS scores on a 100 mm scale (t = time elapsed in minutes)										End-point (min) ¹	VAS score at Endpoint (mm)
	$t=0^*$	$t=1$	$t=15$	$t=30$	$t=45$	$t=60$	$t=75$	$t=90$	$t=105$	$t=120$		
174												
938												
235												
379												

¹The endpoint of the retention time is defined as when the subject has perceived that the effect of the agent has dissipated, or after 2 hours has elapsed. The retention time will therefore be from the time the agent is administered to the endpoint.

* Timepoint before the test agent is administered

Appendix 11 - Subject evaluation of test agent

Chart number: _____ Subject's Initials: _____ Date: ___/___/___

1. How quickly did the product provide relief of your dry mouth symptoms?

- Immediately
- In minutes
- Did not provide relief

Please rate your responses to the following statements by circling the best answer:

2. The taste of the product was tolerable

Strongly disagree Disagree Not sure Agree Strongly agree

3. The thickness of the product was acceptable

Strongly disagree Disagree Not sure Agree Strongly agree

4. I would like to continue using this product

Strongly disagree Disagree Not sure Agree Strongly agree

5. I would purchase this product to use on a regular basis

Strongly disagree Disagree Not sure Agree Strongly agree

6. This product is easy to use

Strongly disagree Disagree Not sure Agree Strongly agree

7. I would prefer using another product

Strongly disagree Disagree Not sure Agree Strongly agree

8. At today's visit, you sampled either a commercially available moisturizing spray or a standard therapy recommended by physicians. Which product do you think you received today?

- Moisturizing spray
- Standard therapy
- Not sure

9. Can you name a preferred product ? _____

10. How long ago did you have anything to eat or drink today? Please choose the best response.

- Less than 1 hour ago
- Approximately 1 hour ago
- Approximately 2 hours ago
- Approximately 3 hours ago
- I did not eat or drink anything this morning

Appendix 12 – Biotène product label/insert with directions for use



Appendix 13 – Phone script addendum for corrective action plan

Investigator:

Hi, my name is [state your name]. I am calling because you participated in a study titled “Duration of effect of moisturizing spray in patients with symptomatic dry mouth” at the University of Rochester’s Department of Dentistry. Do you have a few minutes to discuss the study?

- If yes, continue below.
- If no, ask a better time to call back to discuss the study.

We are calling to let you know that one of the inclusion criteria for the study was that subjects be between the age of 18 and 65 years of age. We wanted to make you aware that you were enrolled into the Biotène study despite your age being outside of the required range at the time of consent. There are no safety issues related to participation over the age of 65 and we are in the process of revising the inclusion criteria to include anyone 18 and older.

Because you were enrolled in error we are requesting your permission to continue to include data related to your participation in this study. Choosing to provide your data, or exclude your data, from the study will not have any impact on your care at Eastman Dental or any other dental/medical setting.

We are only asking that you permit us to use your data that has already been collected for this study. You do not need to participate in any study procedures.

Would you be willing to let us continue to use the data collected for the study?

- If yes, thank them for their time and cooperation.
- If no, thank them for their time and let them know the data will be securely discarded.