Protocol Title
Clinical Evaluation of MucoPEG™ for Xerostomia

Sponsor
SunBio, Inc.

Protocol Number:

SB-MU-001

Version Number:

1.1

November 08, 2021

Confidentiality Statement

This document is confidential and may not be disclosed without prior written consent of SunBio, Inc. This study will be performed in accordance with all stipulations of the protocol and in compliance with all applicable SunBio, Inc. Policies and Procedures.

Study conduct will comply with US FDA Regulations, applicable state and local regulations, and the Good Clinical Practice guidelines.

PROTOCOL APPROVAL PAGE

Protocol Title: Clinical Evaluation of MucoPEG™ for Xerostomia

Protocol Number: SB-MU-001

Date:

We the undersigned, have read and approve the clinical investigational plan specified above and agree on its content:

[redacted] Date

[redacted] Date

[redacted] Date

INVESTIGATOR STATEMENT OF COMPLIANCE

I have read this protocol(s) and agree to conduct and/or supervise the study(ies) in accordance with the relevant, current protocol(s); in accordance with accepted good clinical practice principles and will only make changes in a protocol after notifying SunBio, Inc. .

I agree to obtaining the written and dated approval/waiver of an Institutional Review Board (IRB) prior to initiation of the performance evaluation study and ensure prompt reporting to the IRB of any changes in research activity.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records and to make those records available for inspection to both SunBio, Inc. and regulatory bodies.

I agree to disclose to SunBio, Inc. accurate financial information as required by FDA regulations (21 CFR 54).

I agree to maintain the confidentiality of this study, all study related documents and data; and will not publish or disclose any content without prior written consent.

The signature below attests that I have read and understand the contents of this protocol (or revisions to the protocol) and will adhere to the study protocol requirements as presented including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. Federal Regulations and Good Clinical Practice guidelines.

Investigator Printed Name: _____

Investigator Signature: _____

Date (dd/mmm/yyyy): _____

PROTOCOL REVISION HISTORY

Version	Date	Description of Change	Brief Rationale
1	August 2021	Initial Release	Initial Release
1.1	November 2021	Section 2 Contact Information Section 10.3.3 Device/Product Return Procedure 8.1 Scale	1st Amendment

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1 LIST OF ABBREVIATIONS

TERM	DEFINITION
ADE	Adverse device effect
AE	Adverse event
CDMS	Clinical Data Management System
IRB	Institutional Review Board
CRF	Case Report Form
CRO	Contract research organization
CTA	Clinical Trial Agreement
DD	Device deficiency
DMI	Dry Mouth Inventory
DMP	Data Management Plan
DMRQ	Dry Mouth Relief Questionnaire
eCRF	Electronic Case report form
FAS	Full analysis set
FSFV	First patient first visit
GCP	Good clinical practice
ICH	International Conference on Harmonization
IFU	Instructions for Use
ISF	Investigator's site file
ISO	International Organization for Standardization
PI	Principal investigator
PPAQ	Product Performance and Attributes Questionnaire
PPUQ	Post-Product Use Questionnaire
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System software
SD	Standard deviation
SOP	Standard operating procedure
USADE	Unanticipated serious adverse device effect
VAS	Visual Analog Scale

2 CONTACT INFORMATION

2.1 Sponsor Contact Information

Sponsor:	SunBio, Inc. [redacted]
CRO:	North American Science Associates Inc. [redacted]

3 STUDY SYNOPSIS

Study Number	SB-MU-001
Full Title	Clinical Evaluation of MucoPEG™ for Xerostomia
Short Title	CEMPEG
Protocol Number	SB-MU-001
Protocol Version	Version 1.1
Study Sponsor	SunBio, Inc. [redacted]
Study Purpose	This study will compare the effect of MucoPEG™ to that of Biotène® Dry Mouth Gentle Oral Rinse and evaluate its temporal change in a population of patients with dry mouth symptoms.
Investigational Material/Product	MucoPEG™
Comparative device	Biotène® Dry Mouth Gentle Oral Rinse
Study Objectives	**Primary Objective:** To evaluate the effect of MucoPEG™ in relieving xerostomia, relative to that of Biotène® Dry Mouth Gentle Oral Rinse. Effectof both products will be assessed using the Visual Analogue Scale (VAS) and Dry Mouth Relief Questionnaire. **Secondary Objectives:** • To evaluate the effect of MucoPEG, measured using the Visual Analogue Scale, relative to that of Biotene Dry Mouth Gentle Oral Rinse after two hours and one week of use. • To compare the effect of MucoPEG™ in treating symptoms of dry mouth to that of Biotene®. Effect will be assessed using dry mouth Product Performance and Attributes Questionnaire (PPAQ) and Post-Product Use Questionnaire (PPUQ) • To evaluate the clinical safety of MucoPEG™ • To examine change in the symptoms of xerostomia using the Dry Mouth Inventory (DMI)
Study Design	The proposed study will be an open-label randomized cross-over design. Patients will be randomly assigned to receive either the MucoPEG™ or the Biotène® Dry Mouth Gentle Oral Rinse in the first period. Patients will use the assigned oral rinse two times a day for two weeks. Patients will switch to the other treatment after a wash-out period of one week.

Inclusion Criteria	1. Must have read, understood and signed an informed consent prior to entering the study. 2. Must be 18 years of age or older 3. Good general and mental health with, in the opinion of the investigator or their medically qualified designee, no clinically relevant or significant abnormalities found on examination of the oral cavity or in their medical history. 4. Participant with a Challacombe Scale score of 1 or higher 5. Participant agrees not to eat, drink, chew tobacco, chew gum, smoke, brush or floss their teeth for 2 hours prior to study visits 6. Participant agrees not to use any oral care products or any type of breath mint or lozenges for 2 hours prior to study visits 7. Participant agrees not to consume any food or liquid during the study visits, except for what is provided by the study research staff (e.g., water, MucoPEG™ and Biotène® Dry Mouth Gentle Oral Rinse during evaluation periods) 8. Participant agrees to using clinical oral care supplies provided by the investigators and no other products during the entire study 9. Understands and is willing and able to comply with all study procedures and restrictions
Exclusion Criteria	1. Women who are pregnant or intending to become pregnant over the course of the study, or who have verbally confirmed they are pregnant at the Screening Visit 2. Women who are breast-feeding 3. Participant is currently undergoing radiotherapy and/or chemotherapy. 4. Any condition the investigator identifies that may impede the participant's ability to properly participate in the study. For example, Alzheimer's Disease 5. Participant with untreated oral mucosal disease which in the opinion of the investigator could interfere with the study. For example, presence of oral ulceration. 6. Evidence of gross intra-oral neglect or need for extensive dental therapy 7. Denture wearer (complete dentures) 8. Participant on systemic parasympathetic medications (e.g. pilocarpine) for treating dry mouth, but the dose requirement of which is unstable 9. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or to any of their stated ingredients

	10. Participation in another clinical study (including studies of cosmetic products) or in receipt of an investigational drug within 14 days of the screening visit 11. Previous participation in this study 12. Recent history (within one year prior to screening visit) of alcohol or other substance abuse
Target Population/ Sample Size	42 adults in total for the entire study, males and females
Number of site(s)	Up to 2 sites in the United States
Study Duration	Approximately six months
Participant Duration	The study duration for each participant is expected to be approximately 42 days.
Statistical Methods	Descriptive summaries will be produced for the primary endpoints and the secondary endpoints using data from the intent-to-treat analysis population. Hypothesis testing for the primary endpoints will be carried out using data from the intent-to-treat analysis population and, as a sensitivity analysis, from the per protocol analysis population. Hypothesis tests will be carried out using data on: • the difference in the mean change in VAS for dry mouth • the difference in the proportion of patients rating the relief of dry mouth as "very good" or "excellent" in the Dry Mouth Relief Questionnaire (DMRQ).

4 INTRODUCTION

4.1 Background and Rationale

Xerostomia is a common oral health problem, affecting up to 50% of the population (Furness et al. 2011). Xerostomia is a subjective feeling of dryness of the mouth and can present with or without reduced saliva production (Furness et al. 2011, Villa et al. 2015, Jose et al. 2016). Dry mouth may be associated with other conditions such as diabetes and hypertension. Dry mouth is also a common side effect of many different drugs, such as anti-hypertensives, anti-depressants, decongestants (Tan et al. 2018).

Mouth dryness is commonly associated with other symptoms such as taste disturbances, bad breath and painful mouth ulcers. Dry mouth may also affect speech, chewing and swallowing (Dawes 1987, Furuta et al. 2013).

Current management strategies include symptom relieving measures such as topical saliva substitutes, oral moisturizers, saliva stimulants, and also frequent sips of water. However, the evidence in favour of any particular topical therapy was weak (Jose et al. 2016, Villa et al.2015). Other products (e.g., Biotène®, Hydris™) have became available for treating dry mouth in recent years, but there is an increasing demand for more effective dry-mouth relief products.

[redacted]

5 INVESTIGATIONAL DEVICE DESCRIPTION

MucoPEG™ received FDA clearance on November 5, 2019 with the 510(k) number K190144. MucoPEG™ is an artificial saliva. The main ingredient of MucoPEG™ is a polyethylene glycol (PEG) derivative. This PEG derivative forms a covalent bond with the oral epithelial cell. The

additives to MucoPEG™ are mint (for flavor) and sodium bicarbonate (for pH maintenance when dissolved in water).

MucoPEG™ is available by prescription for home use. It is formulated as a powder and packaged in a single-use packet, which should be kept in a dry environment and stored in the freezer between -4 ± 9 °F. The shelf-life is expected to be one year under the prescribed environment. MucoPEG™ is not sterile and conforms with ISO 10993-1 for cytotoxicity, sensitization, and irritation.

5.1 Intended Use

The device intended use is to relieve the symptoms and discomfort of dry mouth, refresh, moisturize/hydrate, clean, soothe oral irritation, and lubricate oral dryness.

5.2 Dosage

The content of a single dose containing 1 g powder of MucoPEG™ is dissolved in 20 mL (approximately .67 fluid oz) of water using the accessory bottle and shaken well for about 10 seconds for complete mixing. When completely mixed, the solution is gargled and swished inside the oral cavity for 30 - 60 seconds and then spat out. This is followed by rinsing the oral cavity with drinking water to remove any residual product. Users are recommended not to eat or drink for 30 minutes after treatment. MucoPEG™ should be used twice a day, once after breakfast and once before bedtime.

5.3 Labels

The sponsor 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 SB-MU-001 only
SunBio, Inc.
Identifying lot or control number
Study Material name or code designation
Quantity of contents
Expiration date:
“Use as directed”
Storage conditions as indicated in the IFU
Contact details of the site

5.4 Comparator Information

Biotène® Dry Mouth Gentle Oral Rinse is specially formulated to clean, refresh, and relieve dryness and helps soothe oral tissues. Biotène® Dry Mouth Gentle Oral Rinse contains a combination of moisturizers and lubricants to provide immediate and long-lasting dry mouth symptom relief for up to 4 hours, as measured in a 7 day clinical study.
The manufacturers suggests using approximately 15 mL (one tablespoon) of Biotène® Dry Mouth Gentle Oral Rinse, gargle for 30 seconds and then spat out. Biotène® Dry Mouth Gentle Oral Rinse can be used as needed up to 2~3 times a day.

Since Biotène® Dry Mouth Gentle Oral Rinse is a commercially available product, it will be labeled for study use only. Labels will contain the following information:

For use in Study SB-MU-001 only
Identifying lot or control number
Study Material name or code designation
Quantity of contents
Expiration date:
"Use as directed"
Storage conditions as indicated in the IFU
Contact details of the site

6 STUDY PURPOSE

The purpose of this clinical trial is to compare the effect of using MucoPEG™ and its temporal change to those of the Biotène® Dry Mouth Gentle Oral Rinse in patients with xerostomia. This study will also gather data on patient reported outcomes on the safety and performance of the product, mouth-feel qualities and any changes in dry mouth.

6.1 Risk and Benefit Assessment

6.1.1 Risk Minimization

There may be unknown risks for patients participating in this study, however efforts to minimize risks to study patients will be made with the following approaches:

- Conformity with ISO 10993-1 for cytotoxicity, sensitization, and irritation
- Selection of an investigator who is an experienced dental clinician
- Clearly defined inclusion and exclusion criteria will be used to ensure only appropriate patients are enrolled
- Monitoring of investigational sites and patients
- Review of reported Adverse Events

Based on the risk assessment report, the side effects of using the experimental device include:

- Allergic reaction
- Unpleasantness
- Foreign-body sensation

6.1.2 Benefits

There may be no benefit to patients participating in this study, however the data collected in this study may benefit future patients.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective:

To evaluate the effect of MucoPEG™ in relieving xerostomia, relative to that of Biotène® Dry Mouth Gentle Oral Rinse. Effect will be assessed using the Visual Analogue Scale (VAS) and Dry Mouth Relief Questionnaires (DMRQ).

7.2 Secondary Objective(s):

The secondary objectives are as follows:

- To evaluate the effect of MucoPEG, measured using the Visual Analogue Scale, relative to that of Biotene Dry Mouth Gentle Oral Rinse after two hours and one week of use.
- To compare the effect of MucoPEG™ in treating symptoms of dry mouth to that of Biotene®. Effect will be assessed using dry mouth Product Performance and Attributes Questionnaire (PPAQ) and Post-Product Use Questionnaire (PPUQ)
- To evaluate the clinical safety of MucoPEG™
- To examine change in symptoms of xerostomia using the Dry Mouth Inventory (DMI)

7.3 Study Endpoints

The primary endpoint is the difference in the change in the rating of mouth dryness between MucoPEG and Biotene Dry Mouth Gentle Oral Rinse. The rating of mouth dryness is assessed using the Visual Analogue Scale. Its change is the difference between the assessment before using any of the products, on the first day of a treatment period (on Visit 2 and Visit 5), and after the last dose of a product, on the final day of a treatment period (on Visit 4 and 7).

Patients will also be asked to rate the relief of discomfort of dry mouth using the Dry Mouth Relief Questionnaire. The difference in the proportion of patients giving a response of "4 – Very Good" or "5 – Significant/Excellent" between MucoPEG™ and Biotène® Dry Mouth Gentle Oral Rinse will be examined.

The secondary endpoints include examination of the temporal changes in the effect of MucoPEG relative to Biotene, measured using the Visual Analogue Scale, after using the products for two hours (at Visit 2 and Visit 5) and one week (at Visit 3 and Visit 6). Other **secondary endpoints** include assessment of mouth dryness using Product Performance and Attributes Questionnaire (PPAQ - 4 parts), and Post-Product Use Questionnaire (PPUQ) and the Dry Mouth Inventory (DMI).

Data from these sources will be summarised descriptively.

8 STUDY DESIGN

The study is a randomized, open-labelled crossover trial. Each patient receives both the MucoPEG™ and Biotène® Dry Mouth Gentle Oral Rinse treatments.

Patients will be randomly assigned to one of the two groups. Patients in group A will begin with two weeks of treatment (period 1) with MucoPEG™, followed by a wash-out period of one week, and then two weeks of treatment (period 2) with Biotène® Dry Mouth Gentle Oral Rinse. Patients

in group B will receive Biotène® Dry Mouth Gentle Oral Rinse in period 1 and MucoPEG™ in period 2.

8.1 Scale

This study will be conducted at up to 2 clinics in the United States. At least 42 patients meeting the eligibility criteria will be enrolled into the study and followed for approximately 42 days.

8.2 Enrollment

Patients are considered enrolled in the study once they have signed the informed consent. The appropriate Electronic Case Report Form (eCRF) will be completed to document adherence to the inclusion and exclusion criteria.

If a patient fails to meet the inclusion and exclusion criteria, this will be documented and their signed consent form and completed record of inclusion/exclusion criteria will be retained by the Principal Investigator. The patient will not be advanced any further into this clinical investigation.

When a patient is considered eligible for this study, the patient will be assigned an investigational number (patient ID number). This number will be a unique identifier of the patient and documented on the eCRF and all other documentation relating to that patient.

The Principal Investigator (PI) at each site will maintain a master log that will map each patient ID number to the patient's name. This log will remain at the study site and will be confidential.

8.3 Inclusion Criteria

Individuals must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

The inclusion criteria are:

1. Must have read, understood and signed an informed consent prior to entering the study
2. Must be 18 years of age or older
3. Good general and mental health with, in the opinion of the investigator or their medically qualified designee, no clinically relevant or significant abnormalities found on examination of the oral cavity or in their medical history
4. Participant with a Challacombe Scale score of 1 or higher
5. Participant agrees not to eat, drink, chew tobacco, chew gum, smoke, brush or floss their teeth for 2 hours prior to study visits
6. Participant agrees not to use any oral care products or any type of breath mint or lozenges for 2 hours prior to study visits
7. Participant agrees not to consume any food or liquid during the study visits, except for what is provided by the study research staff (e.g., water, MucoPEG™and Biotène® Dry Mouth Gentle Oral Rinse during evaluation periods)
8. Participant agrees to using clinical oral care supplies provided by the investigators and no other products during the entire study
9. Understands and is willing and able to comply with all study procedures and restrictions

8.4 Exclusion Criteria

If a patient meets the exclusion criteria, s/he will not be able to participate in the study.

The exclusion criteria are:

1. Women who are pregnant or intending to become pregnant over the course of the study, or who have verbally agreed that they are pregnant at the Screening Visit
2. Women who are breast-feeding
3. Participant is currently undergoing radiotherapy and/or chemotherapy.
4. Any condition the investigator identifies that may impede the participant's ability to properly participate in the study. For example, Alzheimer's Disease
5. Participant with untreated oral mucosal disease which in the opinion of the investigator could interfere with the study. For example, presence of oral ulceration.
6. Evidence of gross intra-oral neglect or need for extensive dental therapy
7. Denture wearer (complete dentures)
8. Participant on systemic parasympathetic medications (e.g. pilocarpine) for treating dry mouth, but the dose requirement of which is unstable
9. Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or to any of their stated ingredients
10. Participation in another clinical study (including studies of cosmetic products) or in receipt of an investigational drug within 14 days of the screening visit
11. Previous participation in this study
12. Recent history (within one year prior to screening visit) of alcohol or other substance abuse

8.5 Study Duration

The overall study is expected to last around six months and each patient's participation is expected to last around 42 days. Each patient's involvement in the study will last approximately 3 to 5 hours per study visit with a total time commitment expected to be around 30 hours for each patient.

9 STUDY PROCEDURES

9.1 Study Schedule of Events

Table 1 on the next page consists of the scheduled assessments for each study visit.

Table 1: Schedule of Events

			First Treatment 2 times a day for 2 weeks				Second Treatment 2 times a day for 2 weeks		
Assessment	**Visit 1**	**Wash-out period* (7 Days)**	**Visit 2 (Day 1 + 2 Days)**	**Visit 3 (Day 7 ± 2 Days)**	**Visit 4 (Day 14 ± 2 Days)**	**Wash-out period* (7 Days)**	**Visit 5 (Day 22 + 2 Days)**	**Visit 6 (Day 28 ± 2 Days)**	**Visit 7 (Day 35 ± 2 Days)**
Informed Consent	X								
Inclusion/Exclusion	X								
Demographics/Medical History	X								
VAS Measurements			X	X	X		X	X	X
Dry Mouth Relief Questionnaire			X	X	X		X	X	X
Oral Tissue Exam using theChallacombe Scale Score	X		X	X	X		X	X	X
Dry Mouth Inventory			X	X	X		X	X	X
Patient Diary			X	X	X		X	X	X
Intra-Oral Photo **			X	X	X		X	X	X
PPAQ1			X	X	X		X	X	X
PPAQ2			X	X	X		X	X	X
PPAQ3			X	X	X		X	X	X
PPAQ4				X	X			X	X
PPUQ					X				X
Concomitant medication	X		X	X	X		X	X	X
Adverse Events			X	X	X		X	X	X

* Patients must undergo a washout period of at least 7 days prior to using either treatment
**Patients that opt in/consent to having a picture of their mouth taken. Photo must be taken as a pre-use measurement.
For details of the Study Questionnaires, see **Appendix A, B, C, D and E**.

9.2 Visit 1 (Screening Visit)

Patients interested in participating the study will be consented and enrolled at Visit 1. Patients will be consented prior to conducting any study assessments.

The following will be completed at Visit 1:

- Obtain Informed Consent from the patient
- Verify Inclusion criteria has been met and no Exclusion Criteria has been met
- Collect Demographics
- Collect Medical History
- Collect Concomitant Medications
- Conduct the Oral Tissue Exam using the Challacombe Scale Score
- Schedule patient for future study visits

To ensure an effective washout period, the study product will not be provided to the patient during Visit 1 to avoid the patient starting the treatment before obtaining baseline data at Visit 2 (Baseline Visit). **Patients should be reminded to not to use any oral rinse products during the washout period, as described in Section 9.9.**

9.3 Visit 2 (Baseline Visit)

The second visit will be the Baseline Visit and should occur 1 (+2) days after screening visit and could last up to 4 hours as it will collect pre-use and post-use information at multiple timepoints (5 min, 30 min, 60 min, 120 min, and 240 min).

Before starting any treatment, the following **pre-use measurements must be assessed by the Investigator or designated study staff**:

- Visual Analogue Scale (VAS)
- Oral Tissue Exam using the Challacombe Scale Score
- Intra-Oral Photo

Before starting any treatment, the following **pre-use measurement must be completed by the patient**:

- Dry Mouth Inventory (DMI)

Patients will not be allowed to eat or drink during the study visit except for when directed by study staff.

Once the VAS, DMI, the Oral Tissue Exam and Intra-Oral photo have been completed, the sealed envelope will be opened, and treatment order noted. The patient will then self-administer the first dose of the treatment into their mouth using the first sample assigned based on the randomization card.

The **post-use measurements** will include the following at the appropriate timepoints:

- 5 (+ 5) minutes after 1st dose: PPAQ1 (Questions 1-3; completed while patient is in clinic)
- 30 (± 10) minutes after 1st dose: PPAQ2 (Questions 1-11; completed while patient is in clinic)
- 60 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 120 (± 10) minutes after 1st dose: VAS, Dry Mouth Relief Questionnaire (DMRQ), and PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 240 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic or completed at home)

Other Assessments/Schedule of Events that must be completed during Visit 2 include:

- Provide the patient with a patient diary and instructions as indicated below
- Review any changes in concomitant medications
- Review any side effects/adverse events
- Provide the patient with instructions to use the product at home
- Schedule the next follow-up visit (Visit 3) and instruct patients NOT to take the product the morning of Visit 3

Prior to sending the patient home, the patient will be instructed to self-administer the second daily dose into their mouth before bedtime. Patients will be also given a patient diary and instructed to record storage location of the product (i.e. was the MucoPEG™ stored in the freezer as indicated and was the Biotene® stored at room temperature as indicated), the hours of use, and any side effects and/or adverse events they experience while using their assigned study product. Patients will be asked anopen question in their diary about how their mouth feels after using the product.

Patients will be instructed to call the clinic if they experience any adverse side effects and/or adverse events.

Patients will be instructed to use the product at home for 7 days, self-administering 2 doses per day depending on the treatment. They will be scheduled to return to the clinic with their product container and patient diary.

9.4 Visit 3

The third visit should occur 7 (± 2) days after the baseline visit and could last up to 4 hours as it will collect pre-use and post-use information at multiple timepoints (5 min, 30 min, 60 min, 120 min, 240 min).

Before starting any treatment, the following **pre-use measurements must be assessed by the Investigator or designated study staff**:

- Visual Analogue Scale (VAS)
- Dry Mouth Relief Questionnaire (DMRQ)
- Oral Tissue Exam using the Challacombe Scale Score
- Intra-Oral Photo

Before starting any treatment, the following **pre-use measurement must be completed by the patient**:

- PPAQ4 (Questions 15 -23; completed while patient is in clinic)
- Dry Mouth Inventory (DMI)

Patients will not be allowed to eat or drink during the study visit except for when directed by study staff.

The patient will then self-administer the first dose of the treatment into their mouth using the first sample assigned based on the randomization card.

The **post-use measurements** will include the following at the appropriate timepoints:

- 5 (+ 5) minutes after 1st dose: PPAQ1 (Questions 1-3; completed while patient is in clinic)
- 30 (± 10) minutes after 1st dose:PPAQ2 (Questions 1-11; completed while patient is in clinic)
- 60 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 120 (± 10) minutes after 1st dose: VAS, Dry Mouth Relief Questionnaire (DMRQ), and PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 240 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic or completed at home)

Other Assessments/Schedule of Events that must be completed during Visit 3 include:

- Provide the patient with a patient diary and instructions as indicated below
- Review any changes in concomitant medications
- Review any side effects/adverse events
- Provide the patient with instructions to use the product at home
- Schedule the next follow-up visit (Visit 4) and instruct patients NOT to take the product the morning of Visit 4

Prior to sending the patient home, the patient will be instructed to self-administer the second daily dose into their mouth before bedtime. Patients will be also given a patient diary and instructed to record storage location of the product (i.e. was the MucoPEG™ stored in the freezer as indicated and was the Biotene® stored at room temperature as indicated), the hours of use, and any side effects and/or adverse events they experience while using their assigned study product. Patients will be asked a general question in their diary about how their mouth feels after using the product.

Patients will be instructed to call the clinic if they experience any adverse side effects and/or adverse events.

Patients will be instructed to use the product at home for 7 days, self-administering 2 doses per day depending on the treatment. They will be scheduled to return to the clinic with their product container and patient diary.

9.5 Visit 4

The fourth visit should occur 14 (± 2) days after the baseline visit and could last up to 4 hours as it will collect all the pre-use and post-use information at multiple timepoints (5 min, 30 min, 60 min, 120 min, 240 min).

Before starting any treatment, the following **pre-use measurements must be assessed by the Investigator or designated study staff**:

- Visual Analogue Scale (VAS)
- Dry Mouth Relief Questionnaire (DMRQ)
- Oral Tissue Exam using the Challacombe Scale Score
- Intra-Oral Photo

Before starting any treatment, the following **pre-use measurement must be completed by the patient**:

- PPAQ4 (Questions 15 -23; completed while patient is in clinic)
- Dry Mouth Inventory (DMI)

Patients will not be allowed to eat or drink during the study visit except for when directed by study staff.

The patient will then self-administer the first dose of the treatment into their mouth using the first sample assigned based on the randomization card.

The **post-use measurements** will include the following at the appropriate timepoints:

- 5 (+ 5) minutes after 1st dose: PPAQ1 (Questions 1-3; completed while patient is in clinic)
- 30 (± 10) minutes after 1st dose:PPAQ2 (Questions 1-11; completed while patient is in clinic)
- 60 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 120 (± 10) minutes after 1st dose: VAS, Dry Mouth Relief Questionnaire (DMRQ), and PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 240 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14) and PPUQ (**completed while patient is in clinic**)

Other Assessments/Schedule of Events that must be completed during Visit 4 include:

- Collect the patient diary from the patient
- Review any changes in concomitant medications
- Review any side effects/adverse events
- Schedule the next follow-up visit (Visit 5) and instruct patients NOT to use any product as indicated in the Washout Period

After all assessments are completed for Visit 4, the first treatment phase will be considered complete and patients will be instructed to follow the one-week wash-out period, as described in **Section 9.9**.

9.6 Visit 5

The fifth visit should occur 22 (+ 2) days after the baseline visit and could last up to 4 hours as it will collect all the pre-use and post-use information at multiple timepoints (5 min, 30 min, 60 min, 120 min, 240 min).

Before starting any treatment, the following **pre-use measurements must be assessed by the Investigator or designated study staff**:

- Visual Analogue Scale (VAS)
- Oral Tissue Exam using the Challacombe Scale Score
- Intra-Oral Photo

Before starting any treatment, the following **pre-use measurement must be completed by the patient**:

- Dry Mouth Inventory (DMI)

Patients will not be allowed to eat or drink during the study visit except for when directed by study staff.

Once the VAS, DMI, the Oral Tissue Exam and Intra-oral photo have been completed, the patient will then self-administer the first dose of the treatment into their mouth using the second sample assigned. If the patient's randomized first sample was the MucoPEG™ then the second sample assigned to the patient should be the Biotène® Dry Mouth Gentle Oral Rinse and vice versa.

The **post-use measurements** will include the following at the appropriate timepoints:

- 5 (+ 5) minutes after 1st dose: PPAQ1 (Questions 1-3; completed while patient is in clinic)
- 30 (± 10) minutes after 1st dose: PPAQ2 (Questions 1-11; completed while patient is in clinic)
- 60 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 120 (± 10) minutes after 1st dose: VAS, Dry Mouth Relief Questionnaire (DMRQ), and PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 240 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic or completed at home)

Other Assessments/Schedule of Events that must be completed during Visit 5 include:

- Provide the patient with a patient diary and instructions as indicated below
- Review any changes in concomitant medications
- Review any side effects/adverse events
- Provide the patient with instructions to use the product at home
- Schedule the next follow-up visit (Visit 6) and instruct patients NOT to take the product the morning of Visit 6

Prior to sending the patient home, the patient will be instructed to self-administer the second daily dose into their mouth before bedtime. Patients will be also given a patient diary and instructed to record storage location of the product (i.e. was the MucoPEG™ stored in the freezer as indicated and was the Biotene® stored at room temperature as indicated), the hours of use, and any side effects and/or adverse events they experience while using their assigned study product. Patients will be asked a general question in their diary about how their mouth feels after using the product.

Patients will be instructed to call the clinic if they experience any adverse side effects and/or adverse events.

Patients will be instructed to use the product at home for 7 days, self-administering 2 doses per day depending on the treatment. They will be scheduled to return to the clinic with their product container and patient diary.

9.7 Visit 6

The sixth visit should occur 28 (± 2) days after the baseline visit and could last up to 4 hours as it will collect pre-use and post-use information at multiple timepoints (5 min, 30 min, 60 min, 120 min, 240 min).

Before starting any treatment, the following **pre-use measurements must be assessed by the Investigator or designated study staff**:

- Visual Analogue Scale (VAS)
- Dry Mouth Relief Questionnaire (DMRQ)
- Oral Tissue Exam using the Challacombe Scale Score
- Intra-Oral Photo

Before starting any treatment, the following **pre-use measurement must be completed by the patient**:

- PPAQ4 (Questions 15 -23; completed while patient is in clinic)
- Dry Mouth Inventory (DMI)

Patients will not be allowed to eat or drink during the study visit except for when directed by study staff.

The patient will then self-administer the first dose of the treatment into their mouth using the second sample assigned.

The **post-use measurements** will include the following at the appropriate timepoints:

- 5 (+ 5) minutes after 1st dose: PPAQ1 (Questions 1-3; completed while patient is in clinic)
- 30 (± 10) minutes after 1st dose:PPAQ2 (Questions 1-11; completed while patient is in clinic)
- 60 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic)

- 120 (± 10) minutes after 1st dose: VAS, Dry Mouth Relief Questionnaire(DMRQ), and PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 240 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic or completed at home)

Other Assessments/Schedule of Events that must be completed during Visit 6 include:

- Provide the patient with a patient diary and instructions as indicated below
- Review any changes in concomitant medications
- Review any side effects/adverse events
- Provide the patient with instructions to use the product at home
- Schedule the next follow-up visit (Visit 7) and instruct patients NOT to take the product the morning of Visit 7

Prior to sending the patient home, the patient will be instructed to self-administer the second daily dose into their mouth before bedtime. Patients will be also given a patient diary and instructed to record storage location of the product (i.e. was the MucoPEG™ stored in the freezer as indicated and was the Biotene® stored at room temperature as indicated), the hours of use, and any side effects and/or adverse events they experience while using their assigned study product. Patients will be asked a general question in their diary about how their mouth feels after using the product.

Patients will be instructed to call the clinic if they experience any adverse side effects and/or adverse events.

Patients will be instructed to use the product at home for 7 days, self-administering 2 doses per day depending on the treatment. They will be scheduled to return to the clinic with their product container and patient diary.

9.8 Visit 7

The seventh visit should occur 35 (± 2) days after the baseline visit and could last up to 4 hours as it will collect all the pre-use and post-use information at multiple timepoints (5 min, 30 min, 60 min, 120 min, 240 min).

Before starting any treatment, the following **pre-use measurements must be assessed by the Investigator or designated study staff**:

- Visual Analogue Scale (VAS)
- Dry Mouth Relief Questionnaire (DMRQ)
- Oral Tissue Exam using the Challacombe Scale Score
- Intra-Oral Photo

Before starting any treatment, the following **pre-use measurement must be completed by the patient**:

- PPAQ4 (Questions 15 -23; completed while patient is in clinic)
- Dry Mouth Inventory (DMI)

Patients will not be allowed to eat or drink during the study visit except for when directed by study staff.

The patient will then self-administer the first dose of the treatment into their mouth using the second sample assigned.

The **post-use measurements** will include the following at the appropriate timepoints:

- 5 (+ 5) minutes after 1st dose: PPAQ1 (Questions 1-3; completed while patient is in clinic)
- 30 (± 10) minutes after 1st dose:PPAQ2 (Questions 1-11; completed while patient is in clinic)
- 60 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 120 (± 10) minutes after 1st dose: VAS, Dry Mouth Relief Questionnaire (DMRQ), and PPAQ3 (Questions 12-14; completed while patient is in clinic)
- 240 (± 10) minutes after 1st dose: PPAQ3 (Questions 12-14); and PPUQ (**completed while patient is in clinic**)

Other Assessments/Schedule of Events that must be completed during Visit 7 include:

- Collect the patient diary from the patient
- Review any changes in concomitant medications
- Review any side effects/adverse events and resolve if appropriate

After all assessments are completed for Visit 7, the second treatment phase will be considered complete and the subject's participation in the study will be complete.

9.9 Washout Period

Patients will be required to undergo a washout period twice during the study. The first washout period should occur after the subject signs consent and will last until the baseline visit (Visit 2). The second washout period will start after the end of Visit 4 and last until the beginning of Visit 5. A washout period is necessary to ensure patients proceed to a new treatment period without carrying over any residual effects from previous treatment. During the washout period patients will be instructed *not* to use any over the counter or prescription products for dry mouth. Patients will be allowed to only use water to rinse their mouth during the washout period. If a patient uses any type of oral rinse to treat dry mouth during the washout period it will be considered a protocol deviation.

9.10 Patient Diary

Patients will be given a patient diary at Visit 2 and instructed to record storage location of the product (i.e. was the MucoPEG™ stored in the freezer as indicated and was the Biotene® stored at room temperature, as indicated), the hours of use, and any side effects and/or adverse events they experience while using their assigned study product. Patients will also be asked an open question about how their mouth feels after using the product.

9.11 Intra-Oral Photograph

An intra-oral photograph of the mouth will be taken if patients have consented to have their photo taken. The intra-oral photo must be taken prior to administering any study product to the

patient. A total of 5 pictures should be taken as follows: 1) upper side – hard plate 2) tongue 3) buccal mucosa: right side 4) buccal mucosa: left side 5) floor of mouth. Intra-oral photographs will be taken at the designated visits as described in **Table 1.**

9.12 Concomitant Medications

Concomitant medications are prescription medications, over-the-counter (OTC) drugs or dietary supplements taken by a patient. Concomitant medications should be collected at Visit 1 and should include any medications that, in the opinion of the Investigator, could contribute to dry mouth.

10 TRAINING, STORAGE AND ACCOUNTABILITY

10.1 Training Requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, the Sponsor or designated CRO will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities.

10.2 Clinical Study Materials and Clinical Study-Specific Equipment

The sponsor or designated CRO will provide study documentation (e.g. Investigator Site File, eCRF access, Study Worksheets, etc.) and study devices to the site personnel.

The site personnel are responsible to send an acknowledgment of receipt to the sponsor or designee after receiving the study devices (via email or fax).

Where applicable, computer and internet access may be a pre-requisite for site participation.

10.3 Study Device/Product Traceability

10.3.1 Supply of Devices/Products

The study sponsor will have the product shipped directly to the investigational site.

10.3.2 Device Storage and Accountability

Full tracking must be performed as soon as the device/product is received by the investigator/investigation site. Devices/products received by the Site will be confirmed on the shipping documents. The MucoPEG™ provided by the Sponsor will be traced during the clinical study by assigning specific lot numbers, batch numbers, or serial numbers to each device/product.

All information for the use, storage and handling of the investigational device/product as indicated in the Instructions for Use must be taken into account.

10.3.3 Device/Product Return Procedures

The vendor of products manufactured by SunBio Inc., will collect the returned and any malfunction device/product.

11 PATIENT ACCOUNTABILITY AND WITHDRAWAL

11.1 Patient Withdrawals and Discontinuation

During this study, patients may choose to discontinue / leave the study for any of the following reasons:

- Patient's withdrawal of consent.
- Any unexpected adverse effect which, in the opinion of the Principal Investigator, is related to the device and will endanger the well being of the patient if the treatment is continued.
- The deterioration of any underlying illness(es), infection or condition(s) that might interfere with the Clinical Investigation Plan.
- Any problem deemed by the Principal Investigator and/ SunBio, Inc. to be sufficient to cause discontinuation.

Patients who are withdrawn from the study because of an unexpected adverse event will be treated until its resolution. The Principal Investigator will clearly document the date and reason(s) for patient withdrawal in his/her eCase Report Form (eCRF) or EDC system and the monitor must be notified.
Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care. If a patient decides to withdraw, all study tests and procedures will be stopped and the cause of withdrawal will be documented. The investigative site must account for and document all patients enrolled in the study, including those withdrawn from the study or lost to follow-up. If a patient withdraws from the clinical investigation, the reason(s) shall be reported on the eCRF.

Additional study data may no longer be collected after a patient's withdrawal. Data collected up to the point of withdrawal will be used for analysis. Patients who are withdrawn will not be replaced if they have received any of MucoPEG™ or Biotène® Dry Mouth Gentle Oral Rinse doses. Patients will be replaced if they are withdrawn prior to receiving the first dose on Visit 2.

11.2 Loss to Follow-Up

The minimum effort to obtain follow-up information includes 3 attempts to contact the patient (or their legally authorized representative) by telephone, and if not successful, a certified letter sent to the patient's last known address. All contact efforts to obtain follow-up information must be documented in both the patient's medical records and on the eCRFs.

12 SAFETY CONSIDERATIONS

12.1 Investigator Responsibilities

The Investigator is responsible for identifying adverse events 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 patient.

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 patient to the *minimum necessary* standard, i.e. "the minimum necessary to accomplish the intended use, disclosure, or request" [45 CFR 164.502].

12.2 Adverse Event and Device Effect Definitions

The principal measures of safety will be the incidence of adverse events reported during the study. Adverse events will be collected until the subject has exited/withdrawn from the study. Only treatment-emergent adverse event will be collected and reported.

Examples of anticipated adverse events are:

- Temporary and mild, mouth or tongue sensations such as:
    - o Numbness
    - o Burning sensation
    - o Tingling sensations
    - o Taste alteration

The following are definitions related to safety:

Adverse event (AE) means any undesirable clinical occurrence in a patient, 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 or device under study.

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 threat to life, 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 expose the patient to an increased risk of such outcomes 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 the health or safety of study participants, causing hospitalization , or is life threatening or causes death.

Unanticipated adverse device effect is any serious adverse device effect on the health or safety of study participants or any life-threatening problem or death, that is caused by or associated with a device. That effect, problem or death and its nature, severity or degree of incidence was not previously identified in the investigational plan or application. This also included any other unanticipated serious problem which may be associated with a device and is related to the rights, safety and welfare of patients.

12.3 Recording and Reporting

The Investigator records each device-related adverse event on an Adverse Event eCRF. Each record 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 effects/adverse events to the Sponsor using the appropriate eCRF in the EDC system. If the Investigator is not able to report the adverse event or adverse device effect through the EDC system, the Investigator must notify the site monitor or Clinical Study Manager. If the adverse device effect/adverse event is 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 the comparative device is reported to the study monitor and IRB.

12.4 Follow-up of Unresolved Events

All serious adverse events, serious adverse device effects and/or unexpected adverse device effects will be followed up until:

- Thirty days after the onset of the event
- Resolution of the event
- Reaching a stable condition if its effect is a permanent impairment
- The end of a patient's participation in the study

13 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the study is implemented in accordance to the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. The monitor will evaluate study processes and documentation based on the Good Clinical Practice guidelines (GCP). Clinical Monitoring for this study may be performed with a combination of on-site visits and remote sessions. Site monitoring will be conducted under the direction of a separate Clinical Monitoring Plan.

The monitor will be responsible for securing the compliance of the Principal Investigators to the signed agreement, the Clinical Study Protocol, Good Clinical Practice guidelines (GCP), or conditions of approval imposed by the reviewing ethics committee or regulatory authorities.

The Principal investigator will permit a representative from SunBio, Inc. to inspect all eCase Report Forms and corresponding portions of the patient's clinic records and/or original hospital medical records, either on-site or remotely, at regular intervals throughout the clinical investigation. These inspections are for the purpose of verifying adherence to the Clinical Study Protocol and the completeness and accuracy of the data being entered on the eCase Report Forms.

The extent of source data verification is detailed in the monitoring plan. Source data is defined as all the information in the original records, certified copies of the original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Source document are defined as printed, optical or electronic document containing source data, e.g. Hospital records, laboratory notes,

device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

A Principal Investigator found not to be in compliance with the study procedures will receive telephone and/or written notification of the deficiency, which will include a request that deviation be corrected immediately. If the corrections are not made, shipment of products to the institution will be suspended. A request will be made to the Principal Investigator that any products still in his/her possession are returned to SunBio, Inc.

Monitoring for this study will be performed by an appointed CRA from the CRO NAMSA.

14 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

14.1 Responsibility of Investigator

The Principal Investigator is responsible for the proper conduct of the study at their site(s). The investigator will ensure that the study is conducted in compliance with GCP, the protocol, the Clinical Study Agreement, and applicable regulations in 21 CFR Part 812, and any other applicable regulatory requirements.

14.2 Responsibility of Sponsor

The sponsor has the overall responsibility for the conduct of the study, including assurance that the study meets the FDA regulations and other regulatory requirements as applicable.
The sponsor's study-related duties and functions may be transferred to a Contract Research Organization (CRO).

14.3 Auditing

During the running of the clinical investigation, SunBio, Inc. may appoint Quality Assurance (QA) personnel to provide audit of the administration and conduct of the clinical investigation, both at the investigation site and at SunBio, Inc. .
The relevant Regulatory Authority also has the right to conduct an audit of the clinical investigation, that the clinical investigations were, in fact, performed at stated investigation sites and that the data reported to the authority in support of a marketing application accurately reflects the data in the records of the Principal Investigator. The authority also inspects such studies to verify that the clinical investigations were conducted in accordance with Government regulations relating to the Institutional Review Board and Informed Consent. It is the joint responsibility of the Sponsor and the Principal Investigator to ensure the clinical investigation has been conducted in line with all government regulations.
In the event the regulatory authority desires to inspect this clinical investigation, the Principal Investigator will permit authorized inspectors to inspect all facilities and records relating to the clinical investigation and aid the Inspector to perform the audit in a timely fashion.

14.4 Protocol Deviations

A protocol deviation is failure to comply with the requirements specified within the clinical study protocol, ICH GCP, Manual of Operations or IRB requirements. Investigators are not

allowed to deviate from the protocol except when a deviation is necessary to protect patient's rights and well-being, or the scientific integrity of the study (ISO 14155). The noncompliance may be on the part of the patient, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study source documents and promptly reported to SunBio, Inc., or the designated CRO and the local IRB/IEC, according to their requirements. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

In the event that a procedural variation occurs, the SunBio, Inc. should be notified immediately to discuss the required follow-up. Protocol deviations or violations must be documented on the appropriate case report form after discussion with the study monitor.

Data must not be invalidated, eliminated or discarded by the site. All results must be accounted for study source documents.

14.5 Changes to Protocol

In the event the study protocol is amended, the sponsor will provide the Principal Investigator with the protocol amendment(s) and a revised protocol. It is the responsibility of the Principal Investigator to determine if the protocol amendment(s) should be submitted for IRB approval.

Protocol amendments that affect the patient rights, safety, or welfare must be submitted to the IRB for approval. The Sponsor must be notified of the approval, in writing, prior to implementation.

14.6 Reconciliation of Study Material, Supplies and Samples

The Sponsor, via its distributor, will supply sufficient quantities of study materials, supplies and samples to enable the site to complete the study. The site is required to maintain the inventory of these materials provided and document the reconciliation of these materials.

At the completion of this clinical study, all unused materials, supplies, and samples must be returned to the Sponsor or disposed of according to provided instructions. If materials are disposed at the study site, the Investigator must provide the Sponsor with a signed record of disposition.

15 STATISTICAL CONSIDERATIONS

15.1 Sample Size Determination

The primary endpoint is the difference between MucoPEG™ and Biotène® Dry Mouth Gentle Oral Rinse in the reduction of mouth dryness, assessed using the Visual Analogue Scale (VAS), for each patient after using each product for two weeks.

The hypotheses are as follows:

Null hypothesis:
Change in VAS after MucoPEG™ minus change in VAS after Biotène® Dry Mouth Gentle Oral Rinse ≤ 0
Alternative hypothesis:
Change in VAS after MucoPEG™ minus change in VAS after Biotène® Dry Mouth Gentle Oral Rinse > 0

The change in VAS associated with each product for the first treatment period will be calculated as the value of VAS at two hours after the final dose at Visit 4 minus the value of VAS before the first dose at Visit 2. The change in VAS for the second treatment period will be calculated in a similar way using values measured at Visit 5 and 7.

Assuming the average difference between randomization groups is -1.25 with a common standard deviation of 1.50 and a Type I error of 0.05, an effective sample size of 38 patients will provide 80% power to reject the null hypothesis of no difference between the two devices (MucoPEG™ vs Biotène® Dry Mouth Gentle Oral Rinse).

For comparing the percentage of patients giving a response of "Very Good" or "Significant / Excellent" in the Dry Mouth Relief Questionnaire (DMRQ), an effective sample size of 32 patients will provide 80% power to demonstrate theeffect of MucoPEG™ is greater than Biotène® Dry Mouth Gentle Oral Rinse. We assumed a difference in percentages of 0.20 with a standard deviation of 0.45 and a Type I error rate of 0.05.

Since the effective sample size for the VAS scale analysis is greater than that of the Dry Mouth Relief Questionnaire analysis, and effective sample size of 38 patients will be used. Assuming a 10% loss to follow-up, total enrollment for this study is approximately 42 patients.

15.2 Randomization

Patients will be randomly allocated to either group A or group B in this crossover study in a 1:1 ratio. Patients in group A will begin using MucoPEG™ from Visit 2 for two weeks (period 1). This is followed by a washout period of one week. They will switch to using Biotène® Dry Mouth Gentle Oral Rinse from Visit 5 for another two weeks (period 2). Patients in group B will follow the same pattern except they receive Biotène® Dry Mouth Gentle Oral Rinse in period 1 and MucoPEG™ in period 2.

Because of differences in the package of the two products, blinding of treatment allocation in patients is not possible. Study assessors administrating the questionnaires, data entry staff and the statistician may be blinded to the product used at each period.

15.3 Statistical Methods

Data will be summarised descriptively as tables and/or graphs. Continuous variables such as patient's assessment of mouth dryness using the Visual Analogue Scale (VAS) are to be summarised as mean, standard deviation, number of non-missing observations, median, minimum and maximum by the product used (MucoPEG™ or Biotène® Dry Mouth Gentle Oral Rinse) and period (1 – before washout or 2 – after washout). Discrete variables such as ordinal

responses or binary responses (yes or no) from the Dry Mouth Relief Questionnaire, the Product Performance and Attributes Questionnaire, etc. are to be summarised as frequency counts and percentages by product and period.

Measurements of symptom severity will be tested in a Student's t test for the difference between MucoPEG™ and Biotène® Dry Mouth Gentle Oral Rinse in their mean changes in Visual Analogue Scale for each treatment period. Changes between Visit 2 and Visit 4 and between Visit 5 and 7 will be tested for the primary endpoint and changes between Visit 2 and Visit 3, between Visit 5 and Visit 6, within Visit 2 (before the first dose and two hours after the first dose) and Visit 5 (before the first dose and two hours after the first dose) will be tested for the secondary endpoint. Confidence intervals will be presented with significance probability of the difference between the mean values.

Data on other secondary endpoints will be summarised descriptively.

15.4 Analysis of Clinical Data

The intent-to-treat (ITT) analysis population is define as all patients enrolled in the study. Patients in this analysis population will be analyzed according to the group to which they were randomized. The per protocol (PP) analysis population is a subset of the ITT population and excludes those patients with a protocol deviation that could affect the measurement of the primary endpoint. For example, a patient who uses over the counter products for dry mouth during the course of the study.

Descriptive summaries will be produced for the primary endpoints and the secondary endpoints using data from the intent-to-treat analysis population.

Hypothesis testing for the primary endpoints will be carried out using data from the intent-to-treat analysis population and, as a sensitivity analysis, from the per protocol analysis population. The change in VAS associated for each product will be estimated as the value of VAS at the end of a treatment period minus the value of VAS before the first dose in the same period. The difference in mean change in VAS for dry mouth between MucoPEG™ and Biotène® Dry Mouth Gentle Oral Rinse will be tested in a Student's t-test. The difference in the proportion of patients rating the relief of dry mouth as "Very Good" or "Significant / Excellent" will be tested in a binomial test of difference between two proportions. We will consider using statistical methods that are more suitable for smaller sample sizes (for example: exact binomial test, bootstrapping) if they are applicable.

16 SOURCE DOCUMENTS

Study staff will maintain appropriate study records for this study, in compliance with GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. Study staff will permit authorized representatives the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

17 ETHICAL CONSIDERATIONS

17.1 Institutional Review Board (IRB)

Prior to the initiation of this clinical investigation, the Principal Investigator must submit the Clinical Investigation Plan, the Informed Consent Form and any other study documents, as required, to the appropriate IRB for review and approval. The Principal Investigator, and any other member of the investigative team, must not participate in the IRB review of this clinical study. A signed and dated letter granting approval must be provided to SunBio, Inc. or the designated CRO prior to the initiation of the clinical investigation. A list of the voting members of the IRB reviewing this Clinical Investigation Plan may be requested.

17.2 Informed Consent Process

Informed consent is a process that is initiated prior to the patient's agreement to participate in the study and continues throughout the study participation. The Principal Investigator, or designee must explain to each patient the nature of the clinical investigation, including any risks and benefits, its purpose and procedures, and expected duration of involvement in the clinical investigation. Each patient must be informed that participation in the clinical investigation is voluntary and non-participation will not affect his / her right to the treatment the patient is entitled to receive or affect the doctor/clinician-patient relationship. Each patient must be given sufficient time to decide whether they wish to participate and have all their questions addressed prior to signing the IRB-approved consent form(s). A copy of the signed consent form(s) must be provided to the patient. Study specific procedures will not be initiated until the patient has signed the appropriate consent forms(s). Patients have full rights to withdraw from the clinical investigation at any time, irrespective of their initial consent.

Each patient must also give their permission for representatives of the Sponsor, auditor and regulatory authorities to review their hospital records for the purposes of source data verification.

Informed consent from the patient must be obtained in writing before any clinical investigation related procedures are performed.

17.3 Patient Confidentiality

Confidentiality of patient data will be maintained at all times and all documentation relating to a patient will be kept in a secure location.

Study participant's research data will be transmitted to the sponsor. This will not include participant's contact or identifying information. Rather, samples will be de-identified using a study specific number at the time of enrollment. All study forms will be labeled with the study number. No identifiable patient information will be provided to the sponsor or CRO.

Study documents provided to the sponsor will be stored in a secure location with access given to only those that require study access. None of the stored documents will contain any personal identifying information or direct identifiers.

Study files will be made available to the IRB, regulatory authorities, Sponsor (or designee) and/or clinical study staff should they request access for auditing purposes.

18 TERMINATION OF THE CLINICAL INVESTIGATION

In case of a study close-out, the Investigators will be notified by the Sponsor or designated CRO. Appropriate notification/report to IRB will be provided, as required per 21CFR812. After study close-out, the follow-up treatment and medical care of the patients will continue to be as per routine practice of the site.

18.1 Early Termination of the Clinical Investigation

This study may be suspended or prematurely terminated by the sponsor or the investigator immediately upon notice for any cause. Written notification via email or post, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform the IRB/IEC and will provide the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:
• Insufficient adherence to protocol requirements.
• Data that are not sufficiently complete and/or evaluable.
• Determination of futility

19 DATA MANAGEMENT

19.1 Data Collection Methods

Electronic Case Report Forms (eCRFs) will be used to capture data for performance and safety analysis. The clinical database will reside on a production server hosted by iMedNet. Instructions and training for use of the EDC system and proper completion of the forms will be provided to the clinical sites. All changes made to the data will be in an electronic audit trail and available for review. The database will be subject to quality control checks according to the study specific Data Management Plan and NAMSA's standard procedures.

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator or designee. Unanticipated problems must be reviewed by the investigator or designee.

19.2 Completion of Case Report Forms

Source data will be transcribed into the eCRFs of the database. The completed eCRFs must be reviewed and signed by the Investigator. Monitors will review the study database to ensure the validity of the study data relative to the available source documentation.

Once all the patient data has been collected, the analysis and reporting will be conducted. Any data existing for patients who have not received treatment, will not be used in the analysis. Details of these patients will, however, be referenced in the final report.

Any data existing for patients who have received the investigational device/study product, who withdraw voluntarily or who are withdrawn from the clinical investigation, will be used in the final analysis. The inclusion of partial data will be documented in the final report. The final report will be the responsibility of SunBio, Inc. or the designated CRO.

19.3 Review and Return of Completed Documentation

Throughout the clinical study and at the conclusion of the clinical investigation, the electronic case report forms must be signed by the Principal Investigator.

19.4 Retention

The Principal Investigator will retain all copies of the records as directed by SunBio, Inc. for a period of at least 2 years after the latter of the following two dates: the date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting FDA clearance of the product and/or required by local regulations. In all cases, the Principal Investigator must obtain written consent from the Sponsor prior to disposing of any records related to the clinical investigation. Included in records to be maintained are signed Clinical Investigation Plan, copies of the Case Report Forms, signed consent forms, IRB approval letters, product accountability records, correspondence concerning the clinical study and any other documents to identify the patients.

In addition, if the Principal Investigator moves/retires, etc., s/he should provide the Sponsor with the name and address of the person/company that will be responsible for the clinical investigation related records.

20 INVESTIGATOR/INVESTIGATION SITE SELECTION

20.1 Investigator Selection Criteria

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the patients involved in the clinical study. Investigators selected to participate in this study should have previous clinical study experience and must have past experience in the therapy being studied.

20.2 Site Selection Criteria

The following requirements will be evaluated for each investigation site considered for participation in the clinical study:

- Past experience of site staff in conducting clinical studies
- Adequate resources (including study nurse or coordinator), facilities and administrative support for the total study duration
- Site has the capacity to recruit enough patients for the study.
- Computer with access to EDC system

21 PUBLICATIONS AND COMMUNICATIONS

21.1 Clinical Investigation Report

The final report will be compiled by NAMSA, reviewed by SunBio, Inc. and reviewed, approved and signed off by the Principal Investigator.

21.2 Publications

Details of publications will be addressed in each Clinical Trial Agreement.

22 MISCELLANEOUS

22.1 Statement Regarding the Funding of the Study

This Clinical Investigation is a 100% Sponsor funded Investigation.

22.2 Clinical Investigation Agreement

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and returned to the Sponsor or designated CRO prior to the commencement of any clinical study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Sponsor and investigator(s) and be recorded with a justification for the amendments. Furthermore, each Investigator(s) should provide signed Financial Disclosure Forms to disclose a Conflict of Interest.

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APPENDIX A: VAS Questionnaires

Visual Analogue Scale

The Visual Analogue Scale questionnaire will be provided to the patient and the patient will be instructed to rate the dryness of their mouth and tongue by placing a single mark on the line.

1. Rate the dryness of your mouth

0 1 2 3 4 5 6 7 8 9 10

Not dry at all Very dry

2. Rate the dryness of your tongue

0 1 2 3 4 5 6 7 8 9 10

Not dry at all Very dry

APPENDIX B: Dry Mouth Relief Questionnaire

Dry Mouth Relief Questionnaire

The Dry Mouth Relief Questionnaire is given to the patient and they must answer the following q uestion:

Does the product relieve the discomfort of dry mouth?

Please check only one response:

None / (No relief) (1)
Not enough (2)
Some/Good (3)
Very Good (4)
Significant / Excellent (5)

APPENDIX C: Dry Mouth Inventory Questionnaire

Dry Mouth Inventory (DMI)

The Dry Mouth Inventory questionnaire is given to the patient and they must answer the following question:

Please check only one response to each of the following questions:

1. My mouth feels dry

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

2. I have difficulty in eating dry foods

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

3. I get up at night to drink

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

4. My mouth feels dry when eating a meal

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

5. I sip liquids to aid in swallowing food

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

6. I suck sweets or cough lollies to relieve dry mouth

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

7. My lips stick to the teeth

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

8. My tongue sticks to the roof of mouth

   Disagree (0)
   Agree a little (1)
   Agree (2)
   Strongly agree (3)

APPENDIX D: PPAQ & PPUQ Questionnaire

The PPAQ (Product Performance and Attributes Questionnaire) and PPUQ (Post-Product Use Questionnaire) are included below :

PPAQ1: The PPAQ1 Questionnaire is given to the patient 5 (+ 5) minutes after the product is administered. The patient must answer questions 1-3 below while in clinic.

No.	Question item	Answer
1	Relieving the discomfort of dry mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
2	Effectively moistens your mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
3	Effectively lubricates your mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)

PPAQ2: The PPAQ2 Questionnaire is given to the patient 30 (± 10) minutes after the product is administered. The patient must answer questions 1-11 below while in clinic.

No.	Question item	Answer
1	Relieving the discomfort of dry mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
2	Effectively moistens your mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
3	Effectively lubricates your mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
4	Feeling comfortable in the mouth	Poor (1) Fair (2) Good (3)

		Very Good (4) Excellent (5)
5	Soothing your mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
6	Allowing you to speak without difficulty	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
7	Helping to freshen your breath	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
8	Protecting your mouth from drying out	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
9	Providing whole mouth comfort	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
10	Helping you to swallow without difficult	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
11	Helping mouth feel ‘normal’	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)

PPAQ3: The PPAQ3 Questionnaire is given to the patient at three (3) different timepoints (60,120 and 240 minutes).
The first one is given 60 (± 10) minutes after the product is administered and must be completed in clinic. The second one is given to the patient 120 (± 10) minutes after the product is administered and must be completed in clinic. The third one is given to the patient 240 (± 10) minutes after the product is administered and must be completed in clinic or at home. For PPAQ3, the patient must answer questions 12-14 below at each timepoint.

No.	Question item	Answer
12	Having a long-lasting dry mouth relief	Poor (1)

		Fair (2) Good (3) Very Good (4) Excellent (5)
13	Having a long-lasting lubricating effect	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
14	Having a long-lasting moisturizing effect	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)

PPAQ4: The PPAQ4 Questionnaire is only given to the patient at Visits 3, 4, 6 and 7. The patient must answer questions 15-23 prior to using any study product because it is a pre-use measurement. This questionnaire must be completed while the patient is in clinic.

No.	Question item	Answer
15	Providing relief all night	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
16	Reducing the number of times you wake up from dry mouth	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
17	Feeling less parched when you wake up	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
18	Having a long-lasting dry mouth relief	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
19	Having a long-lasting lubricating effect	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
20	Having a long-lasting moisturizing effect	Poor (1) Fair (2)

		Good (3) Very Good (4) Excellent (5)
21	Having an overall dry mouth relief	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
22	Having an overall lubrication effect	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)
23	Having an overall moisturizing effect	Poor (1) Fair (2) Good (3) Very Good (4) Excellent (5)

PPUQ: The PPUQ Questionnaire is given to the patient only at Visits 4 and 7, 240 (± 10) minutes after the product is administered. The patient must answer question 24 below while in clinic.

No.	Question item	Answer
24	Would you continue use of the product?	Yes No

APPENDIX E: The Challacombe Scale

The Challacombe Scale will be provided in a separate document. The Principal Investigator or designee will complete the Challacombe Scale. Per (S Osailan et al, 2011), the Challacombe Scale was developed from research conducted at King's College London Dental Institute under the supervision of Professor Stephen Challacombe. The purpose of this scale is to be able to visually identify and quantify whether your patient has xerostomia (dry mouth) and if so, how it changes over time and the most appropriate therapy options. This scale is applicable whatever your profession. The Challacombe Scale works as an additive score of 1 to 10 : 1 being the least and 10 being the most severe. Each feature scores 1 and symptoms will not necessarily progress in the order shown, but summated scores indicate likely patient needs. Score changes over time can be used to monitor symptom progression or regression.

The Challacombe Scale Score may include the following assessments:

1. Mirror sticks to buccal mucosa 2. Mirrors sticks to tongue 3. Saliva frothy	An additive score of 1 - 3 indicates mild dryness. May not need treatment or management. Sugar-free chewing gum for 15 mins, twice daily and attention to hydration is needed. Many drugs will cause mild dryness. Routine checkup monitoring required.
4. No saliva pooling in floor of mouth 5. Tongue shows generalized shortened papillae (mild depapillation) 6. Altered gingival architecture (i.e. smooth)	An additive score of 4 - 6 indicates moderate dryness. Sugar-free chewing gum or simple sialogogues may be required. Needs to be investigated further if reasons for dryness are not clear. Saliva substitutes and topical fluoride may be helpful. Monitor at regular intervals especially for early decay and symptom change.
7. Glassy appearance of oral mucosa, especially palate 8. Tongue lobulated/fissured 9. Cervical caries (more than two teeth) 10. Debris on palate or sticking to teeth	An additive score of 7 - 10 indicates severe dryness. Saliva substitutes and topical fluoride usually needed. Cause of hyposalivation needs to be ascertained and Sjögrens Syndrome excluded. Refer for investigation and diagnosis. Patients then need to be monitored for changing symptoms and signs, with possible further specialist input if worsening.