SunBio Inc.

Clinical Evaluation of MucoPEG for Xerostomia

Protocol Number: SB-MU-001
Version 1.1 (8th November 2021)

Statistical Analysis Plan

Version 1.1, 22nd May 2023

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	15 Feb 2023	[redacted]	Initial Release.

1.1	22 May 2023	[redacted]	1. Change to hypotheses. We discovered after locking of the database that the hypotheses for the primary endpoint were stated incorrectly in the study protocol version 1.1 because the Visual Analogue Scale was constructed such that 0 = no symptom and 10 = most severe symptom. The original hypotheses were: 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 Since an improvement in symptom was represented by a negative change in its measurement. The hypotheses in this document have been amended to reflect this finding. The corrected version is: Null hypothesis: Change in VAS after MucoPEG minus change in VAS after Biotène ≥ 0 Alternative hypothesis: Change in VAS after MucoPEG minus change in VAS after Biotène < 0 2. Modification to the way change in VAS is assessed as a secondary endpoint. In section 7.3 of the protocol, it is stated that: "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

Version	Version Date	Author/Title	Summary of Key Changes
			hours (at Visit 2 and Visit 5) and one week (at Visit 3 and Visit 6).” This text is ambiguous on the choice of initial value from which the relevant changes are to be measured. Results produced by calculating changes between two successive time points were examined by the Sponsor. The Sponsor requested that changes to be calculated from the baseline value, before any of the products were used after their examination.

Document Approval

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Table of Contents

1 Introduction

This statistical analysis plan describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol "Clinical Evaluation of MucoPEG for Xerostomia". This statistical analysis plan should be read in conjunction with the study clinical investigation plan and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol "Clinical Evaluation of MucoPEG for Xerostomia", Version 1.1 (8th November 2021). Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the statistical analysis plan.

Applicable Documents:

Document Number, Version	***Document Title***
SB-MU-001 Version 1.1	Clinical Evaluation of MucoPEG for Xerostomia (CEMPEG)

1 Abbreviations

Abbreviation/Term	***Definition***
AE	Adverse events
CRF	Case report form
DMI	Dry Mouth Inventory
DMRQ	Dry Mouth Relief Questionnaires
PPAQ	Product Performance and Attributes Questionnaire
PPUQ	Post-Product Use Questionnaire
SAE	Serious adverse events
VAS	Visual Analogue Scale

2 Study Objectives

2.1 Primary Objective

To evaluate the effect of MucoPEG (the investigational product) relative to that of Biotène Dry Mouth Gentle Oral Rinse (the comparator) in reliving xerostomia. This effect will be assessed using:

- The Visual Analogue Scale (VAS)
- The Dry Mouth Relief Questionnaires (DMRQ)

2.2 Secondary Objective

- To evaluate the effect of MucoPEG relative to that of Biotène Dry Mouth Gentle Oral Rinse, using the Visual Analogue Scale, after two hours and one week of use.
- To compare the effect of MucoPEG in treating symptoms of dry mouth to that of Biotène Dry Mouth Gentle Oral Rinse, using the dry mouth Product Performance and Attributes Questionnaire (PPAQ) and the 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).

2.3 Primary Endpoints

- The difference between MucoPEG and Biotène Dry Mouth Gentle Oral Rinse in the change in rating of mouth dryness.

  Mouth dryness will be measured using the Visual Analogue Scale:

  - VAS (before), which is measured before using any of the products on the first day of each treatment period, at Visit 2 or Visit 5
  - VAS (end), which is measured after the last dose of a product on the final day of each treatment period, at Visit 4 or Visit 7

  Change in the rating of mouth dryness is the difference between the two time points, that is, VAS (end) – VAS (before).

- The difference between MucoPEG and Biotène in the relief of sensation of mouth dryness between Visit 2 and Visit 4 in the first treatment period and between Visit 5 and Visit 7 in the second treatment period.

  This will be measured using the Dry Mouth Relief Questionnaire to evaluate the proportion of patients giving a response of “4 – very good” or “5 – significant / excellent”.

2.4 Secondary Endpoints

- The difference between MucoPEG and Biotène Dry Mouth Gentle Oral Rinse in the change in rating of mouth dryness.

  Mouth dryness will be measured using the Visual Analogue Scale:

  - VAS (before), which is measured before using any of the products on the first day of each treatment period, at Visit 2 or Visit 5

- VAS (after), which is measured two hours after using any of the products on the first day of each treatment period, at Visit 2 or Visit 5
- VAS (1 week), which is measured after the last dose of a product at one week in each treatment period, at Visit 3 or Visit 6

Change in the rating of mouth dryness is the difference from before the products were used, that is, VAS (after) – VAS (before) and VAS (1 week) – VAS (before).

- Assessment of mouth dryness using the Product Performance and Attributes Questionnaire (PPAQ):
  - PPAQ1, PPAQ2 and PPAQ3 at Visit 2, 3 and 4 in Period 1 and at Visit 5, 6 and 7 in Period 2. Patients are to be assessed using PPAQ1 once at 5-10 minutes after administration of the product in each visit, PPAQ2 once at 30±10 minutes, and PPAQ3 three times at 60±10 minutes, 120±10 minutes and 240±10 minutes at each visit.
  - PPAQ4 at Visit 3, 4 in Period 1 and Visit 6, 7 in Period 2.
- Assessment of mouth dryness using the Post-Product Use Questionnaire (PPUQ) at Visit 4 in Period 1 and at Visit 7 in Period 2.
- Assessment of mouth dryness using the Dry Mouth Inventory (DMI) at Visit 2, 3 and 4 in Period 1 and at Visit 5, 6 and 7 in Period 2.

3 Study Design

This study is a randomized, open-labelled crossover trial. Each patient will receive both MucoPEG and Biotène Dry Mouth Gentle Oral Rinse. This study will take place in up to two study sites.

3.1 Randomization

Patients will be randomized at Visit 1, after they have signed the consent form and have been confirmed that they had fulfilled the criteria for study inclusion and exclusion. A unique investigational number will be assigned to each patient as the study identifier after they have entered the study.

Patients who leave the study between signing the consent form and randomization will be replaced. But patients who leave the study after randomization are considered to be lost to follow-up and will not be replaced.

Each patient will be allocated with equal probability within blocks of six patients to one of:

- Group A: to receive MucoPEG in Period 1 and Biotène in Period 2

- Group B: to receive Biotène in Period 1 and MucoPEG in Period 2

Each period will last two weeks. There will be a washout period of one week between Visit 1 and Period 1 and between Period 1 and Period 2, during which patients will only use plain water as mouth rinse.

3.2 Blinding

This is an open-labelled study. The product packaging is different and cannot be changed. Therefore, patients are not blinded to treatment allocation.

Study assessors administrating the questionnaires, data entry staff and the statistician may be blinded to the product allocation at each period.

3.3 Study Assessments

Patients are considered to be enrolled in this study after placing their signature on the consent form at Visit 1. Their eligibility to proceed and their concomitant medications will then be checked. Before Period 1 (the first use of MucoPEG or Biotène), patients will undergo one week of "washout" period.

During Period 1, which will last for two weeks, patients will use one of the products twice daily and will be assessed on the first day (Visit 2), seventh day (Visit 3) and fourteenth day (Visit 4) using the VAS, DMRQ, DMI, PPAQ, PPUQ. Information from symptom diary, medications, clinical examination and adverse events will also be recorded.

Another washout period of one week follows Period 1. The assessments for the second treatment will have the same pattern, with Visit 5, 6 and 7 to take place within Period 2.

4 Sample Size Determination

The hypotheses for this study are

- Null hypothesis
  Change in VAS after MucoPEG minus change in VAS after Biotène ≥ 0
- Alternative hypothesis
  Change in VAS after MucoPEG minus change in VAS after Biotène < 0

The change in VAS associated with each product 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 for the first treatment period. Since the Visual Analogue Scale is constructed such that 0 = no symptom and 10 = most severe symptom, an improvement in symptom is represented by a negative change in its measurement. The hypotheses are to test whether patients would experience greater improvement in their symptoms after a course of MucoPEG.

The change in VAS for the second treatment period will be calculated in a similar way from the value of VAS before the first dose at Visit 5 and the value of VAS at two hours after the final dose at Visit 7.

Assuming the average difference between randomization groups is -1.25, a common standard deviation of 1.50 and a Type I error of 0.05 (one-sided probability), an effective sample size of 38 patients will provide 80% power to reject the null hypothesis of no difference between the two products (MucoPEG versus Biotène).

For comparing the proportion of patients giving a response of "Very Good" or "Significant / Excellent" in the Dry Mouth Relief Questionnaire, an effective sample size of 32 patients will provide 80% power to demonstrate a clinical improvement associated with MucoPEG over Biotène. We assumed a difference of 0.20 between the proportions, a standard deviation of 0.45 and a Type I error rate of 0.05.

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

5 Statistical Analyses

5.1 General Considerations

Unless specified otherwise, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely accepted statistical or graphical software.

5.1.1 Descriptive Statistics

Continuous data will be summarized as mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized as frequency counts and percentages.

Confidence intervals may be estimated, where appropriate, using the t-distribution for continuous data and the score method for categorical variables.

5.1.2 Study Day

Study day 1 is the date when each patient in this study takes the first dose of MucoPEG or Biotène, the product a patient has been randomly allocated to, in Period 1. Day in study will be calculated relative to the first dose of MucoPEG or Biotène in Period 1 as follows:

Study Day = 1 + Assessment Date – Date of the first dose of MucoPEG or Biotène in Period 1

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit (including death).

Duration variables will be calculated as follows:

Duration = 1 + Date of Event of Interest – Date of the first dose of MucoPEG or Biotène in Period 1

5.1.3 Visit Windows

Unless otherwise specified, visit based assessments will be analysed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

5.1.4 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at 0.05 significance level. P-values will be rounded to two decimal places. If a p-value is less than 0.001 it will be reported as “<0.001”.

5.1.5 Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to one decimal place. Percentages <0.05% will be reported to two decimal places. For continuous parameters, means and medians will be reported to one additional decimal place than the measured value while standard deviation will be reported to two additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

5.2 Analysis Populations

The following sets are defined for analysis:

1. **Eligible patients**: Patients who have signed the consent form and fulfilled all inclusion and exclusion criteria.
2. **Intent-to-treat set**: Patients who have received at least one dose of MucoPEG or Biotène during the study.
3. **Per Protocol set**: A subset of the full analysis set without any major protocol deviations.

The primary analysis set will be the intent-to-treat set with all other sets to be used for supportive analysis. Supportive analysis for the primary endpoints will be performed using the per protocol set to provide insight into the potential impact of any protocol deviations on the primary results of the study. If a per protocol set is the same as the intent-to-treat set, the results will be the same and the analyses will not be repeated for that supportive analysis set.

5.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. If a data point is missing, that data point will not contribute to that portion of the analysis. The number of evaluable observations will be reported so that the extent of missing data can be assessed.

In the case of a date (such as partial adverse event onset or death), the unknown portion of the date will be imputed. If the month and year are known, the 15th of the month will be used for analysis. If only the year of birth is known, date of birth will be analysed as if it occurred on 30th June of the known year. In all other cases, unknown dates will be referred to study sites for resolution.

Imputation of partial dates is subject to the condition that it must occur on or after the date of Visit 1. In the case where the imputed date is prior to the date of Visit 1, the date of Visit 1 will be used.

Since death cannot occur before any documented subject contact, for date of death the imputed date of death must occur on or after last known contact in study.

5.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each visit specified in the protocol. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

5.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic, medical history, and clinical characteristic variables.

5.6 Analysis of Study Endpoints

5.6.1 Primary Analysis

The primary endpoint will be examined in the following hypothesis:

- Null hypothesis
  Change in VAS after MucoPEG minus change in VAS after Biotène ≥ 0
- Alternative hypothesis
  Change in VAS after MucoPEG minus change in VAS after Biotène < 0

The change in VAS associated with each product 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 for the first treatment period. Since the Visual Analogue Scale is constructed such that 0 = no symptom and 10 = most severe symptom, an improvement in symptom is represented by a negative change in its measurement. The hypotheses are to test whether patients would experience greater improvement in their symptoms after a course of MucoPEG.

The change in VAS for the second treatment period will be calculated in a similar way from the value of VAS before the first dose at Visit 5 and the value of VAS at two hours after the final dose at Visit 7.

This set of hypotheses will be tested in a one-sided test of difference between two means, for each treatment period, to examine whether a greater change in VAS is associated with MucoPEG than with Biotène. Interval estimation will be carried out using the t distribution and the objective will be met if the upper limit of a 90% confidence interval of the difference is less than zero.

The primary endpoint will also be examined in the following hypothesis:

- Null hypothesis
  The proportion of patients with a favourable response after MucoPEG minus the proportion of patients with a favourable response after Biotène ≤ 0
- Alternative hypothesis
  The proportion of patients with a favourable response after MucoPEG minus the proportion of patients with a favourable response after Biotène > 0

The numerator will be the number of patients who responded with “4 – very good” or “5 – significant / excellent” in the Dry Mouth Relief Questionnaire. The denominator will be the number of patients eligible for taking the Dry Mouth Relief Questionnaire. Patients with missing outcome status will be reported as a separate category. Change in proportions between Visit 2 and Visit 4 in the first treatment period and between Visit 5 and Visit 7 in the second treatment period will be assessed.

This set of hypotheses will be tested in a one-sided test of difference between two proportions, for each treatment period, to examine whether a greater proportion is associated with MucoPEG than with Biotène. Interval estimation will be carried out using an exact method for binomial outcomes and the objective will be met if the lower limit of a 90% confidence interval of the difference is greater than zero.

The endpoint will be evaluated by analysing the data from the intent-to-treat set. The endpoint will be presented as the mean difference in scores and its one-sided confidence interval for change in VAS and as mean difference in proportions for ratings from the Dry Mouth Relief Questionnaire.

5.6.2 Sensitivity Analysis

If the proportion of missing responses in the primary endpoints exceeds 5%, we may consider imputing every missing response in favour of Biotène. The same method as outlined in section 5.6.1 will be used for analysing the imputed datasets and the results will be compared to assess the robustness of our conclusions against missing responses.

5.6.3 Secondary Endpoints

Data on each of the secondary endpoints will be summarized descriptively by each product and by treatment period and study site. Estimates of statistics will be presented with their confidence intervals for:

1. The effect of MucoPEG in period 1
2. The effect of MucoPEG in period 2
3. The effect of MucoPEG, combining period 1 and 2
4. The effect of Biotène in period 1
5. The effect of Biotène in period 2
6. The effect of Biotène, combining period 1 and 2

Continuous endpoints such as change in the rating of mouth dryness, measured as the change in VAS, will be summarized as mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical endpoints such as responses in Product Performance and Attributes Questionnaire, Post-Product Use Questionnaire and Dry Mouth Inventory will be summarized as frequency counts and percentages.

5.7 Poolability Analysis

Patients may be recruited from up to two study sites. In the case that all the patients in this study are recruited from only one site, poolability analysis is not applicable. However, if more than one study site is involved, we may present the results stratified by study sites.

5.8 Safety Analyses

Adverse events (AE) will be reported for the intent-to-treat set. AEs will be tabulated with the number of events and affected patients for each event type and for all types combined. Rates will be reported as the number of patients who experience at least one event during the analysis interval out of the total number of patients with follow-up to the beginning of the analysis interval. Serious adverse events will

also be tabulated. The rate of all AEs and SAEs reported in the study will be reported by product and by treatment period.

All AEs and SAEs will also be summarized by relatedness to the products under investigation as described above. Details of such events will also be reported in listing format.

5.9 Subgroup Analyses

Analyses will be stratified by study site. Subgroup analysis of the primary endpoints will be carried out for sex and age group (below the median age of the study sample versus above the median age). These analyses are intended to demonstrate consistency of results across subgroups.

Heterogeneity between subgroups will be examined in a regression model that includes the treatment, subgroup and their interaction. Additional exploratory analysis may be performed to understand any variations in the outcomes between subgroups.

5.10 Interim Analyses

No interim analyses are planned.

5.11Protocol Deviations

Deviations from the procedures outlined in the protocol will be reported on the CRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

6 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

7 Subject Listings

Subject listings will be provided for protocol deviations and for patients experiencing any side effects or adverse events.