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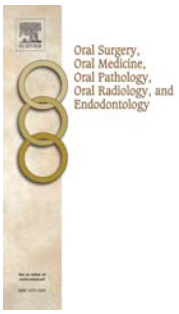


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**TITLE PAGE**

**A Phase II Clinical Trial of Natural Formulation Containing Tea Catechins for Xerostomia**

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**ABSTRACT**

Previous animal studies indicated catechins from the tea plant (*Camellia sinensis*) may modulate salivary function and possess a therapeutic effect for xerostomia. The objective of this study was to evaluate a natural formulation containing tea catechins in 60 xerostomia patients, including patients with Sjogren's syndrome, using a double blind, placebo-controlled, randomized design. The functional placebo contained all natural formulation ingredients and 500 mg xylitol, but without the key plant extracts. After 8 weeks of therapy, the xylitol-containing placebo failed to modulate saliva output. In comparison, the catechin-containing natural formulation resulted in a statistically significant increase in un-stimulated (3.8-fold) and stimulated (2.1-fold) saliva output verses baseline. The quality of life score showed a significant improvement in both groups, but no significant difference between groups. In conclusion, the catechin-containing natural formula partially restored salivary function in xerostomia patients and provided an objective improvement in saliva output, which warrants large-scale clinical trials.

Key Words

Saliva, Oral Medicine, Clinical Studies/Trials, Sjogren's Syndrome, Green Tea Catechins, Xerostomia.

## INTRODUCTION

Xerostomia (the perception of dry mouth) affects up to 40% of US adults during their lives, and can have a major negative impact on quality of life [1, 2]. Causes of xerostomia include chronic medication use, diabetes, and Sjogren's syndrome (SS). Current treatments, such as artificial lubricants, are primarily palliative, at best providing just some of the protective functions of saliva [3]. Prescription cholinergic agonists to stimulate salivary function often have significant side effects [1, 4, 5). Thus, novel approaches to prevention and therapy for xerostomia are in urgent need [6].

Green (i.e., unfermented) tea polyphenols (GTPs) are a group of polyphenolic compounds present in the leaves of the tea plant. Several lines of evidence are consistent with a beneficial role for green tea phytochemicals, particularly GTPs, in xerostomia and SS (as well as other autoimmune diseases) [7]. Considerable differences in the prevalence of xerostomia and SS exist between various regions and communities, and both conditions are lower in green tea-consuming countries relative to the US [7]. Importantly, GTPs reduce glandular histopathology in NOD/Lt mice (a model for secondary SS), with significantly smaller glandular lymphocytic infiltrates [8]. We discovered that (-)-epigallocatechin-3-gallate (EGCG, the most potent GTP) suppressed expression of various (often SS-associated) autoantigens in cultured cells. Additionally, EGCG suppressed salivary gland epithelial cell proliferation/repair marker levels significantly, and reduced the modest level of apoptosis in NOD mice [8]. This effect is associated with an up-regulation of p21 [9]. Recently, we found that expression of the antioxidant enzymes catalase and peroxiredoxin 6 was reduced in NOD mouse salivary glands, and EGCG normalized their

levels [10].

Evidence from *in vitro* and *in vivo* studies suggests that GTPs/EGCG could provide a natural and effective approach to xerostomia management, and could delay disease progression of salivary dysfunction, and partially restore salivary function, acting through molecular and cellular-based mechanisms in the salivary glands. We hypothesized that a proprietary natural formula containing tea catechins would be effective in modulating salivary function in patients with xerostomia. The objective of the current study was to clinically test the effect of this formula on objective salivary flow rates and subjective quality of life in a double blind, placebo controlled, randomized trial to collect information for future large trials designed to provide the basis for an important alternative approach using plant-derived, non-toxic compounds to treat xerostomia patients without adverse effects.

## STUDY DESIGN AND METHODS

This clinical study used a double blind placebo-controlled design involving 60 patients (30 placebo control and 30 study drug) with subjective complaint of dry mouth (xerostomia), including SS-mediated salivary gland hypofunction. This number was based on a power analysis using estimates of the coefficient of variation for stimulated whole salivary flow rate (SWSFR, 0.63) and un-stimulated whole salivary flow rate (UWSFR, 1.10). A sample size of n = 30 subjects per group would yield 80% power for detecting an improvement of at least 33% in SWSFR and 58% in UWSFR from baseline to Week 4 or Week 8 when comparing active treatment *versus* placebo using a significance level of 0.05.

*Study population and recruitment*

The clinical protocol, with full Informed Consent, was approved by a full Human Assurance Committee review at Georgia Regents University (GRU). The study was registered in clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01647737). Patients were recruited with a primary complaint of oral dryness. A detailed chart review was performed for potential study subjects with xerostomia within the patient population in the Center of Oral Medicine at GRU College of Dental Medicine. Charts were reviewed based on ICD 9 code 527.7 [n= 397]. External references and volunteers [n= 12] outside the Oral Medicine practice were also considered for eligibility. Eligibility was assessed based on defined inclusion and exclusion criteria (Table 1). Potential study subjects identified by this process [n= 86] were contacted for possible study recruitment. Sjogren's diagnoses and histologic findings were evaluated using the

2002 classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. A biopsy was determined to be consistent with Sjogren's if there was a focus score of greater than or equal to 2.0. Recruitment was continued on a rolling basis throughout an 18 month period.

*Test article*

Each intervention lozenge (manufactured by Nomax, St. Louise, MS) contained a proprietary natural formula [referred to as the MighTeaFlow (MTF) formula] of a combination of two plant extracts including green tea catechins. The placebo contained all other ingredients, including 500 mg xylitol, except for the MTF formula. The test and placebo lozenges were designed with identical color, taste and texture. Subjects were instructed to take one lozenge every four hours (maximum 6 lozenges/day) during the day over an 8 week period. Subjects were evaluated at the same time of day for all visits and lozenges were used on the day of a visit. Side effects were evaluated at each visit by assessing the subjects' response to the following question "Did you have any adverse reactions to the lozenges? If so, what?"

*Blinding*

The placebo and test material had an identical appearance and were packaged identically, with the intervention coded as A and placebo as B: only one person (SH, who was not involved in patient care) controlled the code, and all clinical staff and subjects were blinded to the treatment. Blinding was revealed after all subjects completed the trial and all statistical data were collected.

*Visit Schedule, data collection and management.*

Patients with a subjective complaint of xerostomia were asked to complete a screening questionnaire. Based on their responses, if they met the study criteria the study coordinator was notified and met with the patient either immediately or at a scheduled follow-up appointment. After review of the screening form information and verification that the patient was eligible for the study, the details of the study were explained to the patient and informed consent obtained. Demographic, medical history, and contact information were collected; missing information was noted for follow-up investigation by the study coordinator. The study data collection schedule is shown in Figure 1. Data collection was *via* paper forms and subsequently scanned into the patient's secure electronic health record stored in an Axium data management system. Appropriate measures were taken to protect the privacy of the subjects and maintain confidentiality of study data according to GRU policy. Patients eligible for the clinical trial were randomly assigned to two groups using block randomization with blocks of size 6. The randomization scheme was obtained using the www.randomization.com website (accessed October 7, 2011). Compliance was measured at each visit by subtracting the remaining lozenges in the kit from the amount dispensed at each visit divided by the number of days between visits.

*Quality of Life Assessments*

A questionnaire containing 7 questions were provided to the subjects to be completed at each visit. A 100-mm visual analog scale (VAS) was used to record the responses to each of the first 6 questions addressing the study participant's degree of oral dryness (Table 2). The VAS was arranged with negative responses on the left and positive responses on the right. The patients marked their responses on a 100 mm scale in relation to these extremes and the distance in mm from the leftmost portion of the scale was measured. This QOL measure is considered related to

the severity of xerostomia complaint and the impact it has. The scores on the 5 items were totaled to obtain the total quality-of-life (QOL) score. In the statistical analysis, the score at baseline was subtracted from the later scores to assess change.

*Saliva collection*

Un-stimulated saliva collection was performed before stimulated saliva collection. Patients were asked to fast for a minimum of 90 minutes before saliva collection with no stimulation (smoking, tooth brushing, drinking, or chewing gum). They also fasted from lozenge use during this time. Saliva collection took place in a climate-controlled facility, with the patient sitting in a comfortable chair, bending forward slightly with an open mouth, allowing un-stimulated saliva to collect passively into a funnel placed in the saliva collecting tube for a period of five minutes. Salivary flow rates were collected at the same time of day for all four collections. The saliva volume was determined by tube weight difference. Stimulated saliva collection took place five minutes after un-stimulated saliva collection. Each patient was given a piece of neutral wax to chew 45 times to stimulate flow. Saliva was collected and quantified in the same way as for un-stimulated saliva. In the statistical analysis, the salivary flow rates at baseline were subtracted from the flow rates at the later time points in order to assess change.

*Statistical Methods*

Data were analyzed separately for each of the outcomes in this study: SWS, UWS, and QOL. The data were analyzed in an intent-to-treat manner, with each study subject retained in the treatment group to which they were originally assigned (MTF lozenge or placebo lozenge). No special techniques (e.g., last observation carried forward, multiple imputation, etc.) were used

to account for missing data. Mixed-effects models (as implemented in PROC MIXED in SAS) were used to carry out the repeated measures analyses described below. These analyses enable one to make use of all available data, even for subjects whose data were missing at certain time points (due to dropout or other reasons), with no special accommodation for missing observations required as long as the missing data can be assumed to be missing at random. There was no reason to believe otherwise in the present study.

For each outcome, change scores were calculated for Visits 2, 3, and 4 by taking the difference between the value at baseline and the value at each visit. These change scores were analyzed using repeated measures analysis of variance with one grouping factor at two levels (treatment: MTF lozenge, placebo) and one repeated factor at 3 levels (visit: 2, 3, 4). The purpose of the repeated measures analysis was to determine if there was a significant difference in mean change score between the two treatments over the course of the study, and if there was a significant difference in mean change from baseline between visits 2, 3, and 4. The Tukey-Kramer method for repeated measures was used to test all pairwise comparisons among the three visits.

If a significant interaction was found between treatment and visit, a simple-effects analysis was performed in which the two treatments were compared separately at each visit, and the three visits were compared separately for each treatment. Bonferroni adjustments were made so that the family-wise error rate for the tests of each factor would be controlled at the 0.05 level.

For each of the outcomes, the change scores were tested for normality using the Shapiro-Wilk test. Because the normality assumption was violated for the changes scores for each outcome (SWS, UWS, QOL), a rank-based analysis was used instead of the traditional repeated measures analysis.

Unless otherwise specified, two-tailed tests with a significance level of 0.05 were used for all comparisons. Summary statistics are given as mean ± S.D. All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC, 2010).

## RESULTS

*Participant flow*

Of the 60 participants who were initially recruited and randomly assigned to the two material study groups (30 each), 51 had complete data for the primary outcomes of SWS and USWS flow rates. However, the statistical analysis made use of all available data in an intent-to-treat manner. Nine subjects (four intervention, five placebo) did not complete the trial: one for personal reasons, one because of a long commute to the study site, two due to medical reasons, three from non-compliance, unwilling to continue, or non-return, and two due to allergy. These two patients described itching and scratchy sensations in their mouth and throat. No clinical signs of an allergic reaction were evident. Based on the clinical history of symptoms, their complaints were most likely due to allergic rhinitis for airborne allergens and not related to the lozenge. We did not anticipate any adverse reactions or events in this study and relied on subject self reporting to the PI. During the entire trial period, no harmful side effects or adverse events were reported.

*Baseline data*

The 60 patients recruited comprised 58 females and 2 males. The age ranged between 21 and 74 years (Table 3). Duration of xerostomia ranged from 4 months to a long standing history. Ninety-one percent of subjects had tried over-the-counter medications for xerostomia and/or sialogogues prior to study. Subjects who were on sialogogues underwent a washout period of 1-2 weeks prior to entering the study recruitment. Subjects on greater than three xerostomia-causing medications were excluded from study. There were no significant differences between the average number of xerostomia-causing medications between the study and placebo groups.

*Numbers of subjects analyzed*

In Group A (intervention, using the MTF lozenge), 26 of 30 patients completed the 8 week study. In Group B (control, using the placebo lozenge), 25 of 30 patients completed the study. In both groups, each patient consumed one lozenge every 4 hours during the day with a maximum of 6 lozenges daily.

*Stimulated whole saliva (SWS) flow rate*

In the rank-based repeated measures analysis for change in SWS flow rate, the interaction between treatment and visit was not significant ($p = 0.592$), so main effects were analyzed. The main effect for group was significant ($p = 0.005$), but the main effect for visit was not ($p = 0.471$). Thus, there was a significant difference in improvement in SWS flow rate between the two groups over the entire course of the study. Subjects in the intervention group experienced a fold increase in saliva flow of 1.5, 1.7 and 2.1 relative to baseline at week 1, 4, and 8 respectively. In the placebo group, there was no meaningful change in stimulated saliva flow rate throughout the trial period (Table 4A).

*Un-stimulated whole saliva (UWS) flow rate*

In the rank-based repeated measures analysis for change in UWS, the interaction between treatment and visit was not significant ($p = 0.920$), so main effects were analyzed. The main effect for group was significant ($p = 0.002$), but the main effect for visit was not ($p = 0.335$). Thus, there was a significant difference in improvement in UWS flow rate between the two treatments over the entire course of the study. Subjects in the intervention group experienced a

fold increase in un-stimulated saliva flow rate of 3.3, 3.1 and 3.8 relative to baseline at week 1, 4, and 8 respectively**.** Visits 2, 3, and 4 did not differ significantly in terms of improvement in UWS. In the placebo group, there was no meaningful change in un-stimulated saliva flow rate throughout the trial period (Table 4B**)**.

Quality of Life and Statistical Analyses

Detailed summary statistics and analyses for the quality of life surveys are presented in the online supplement. For each question of the questionnaire, the interaction between treatment and visit was not significant. Overall, for questions 3, 4, and 5, there was no significant main effect on the change of QOL for treatment groups or visits, and there was no significant difference between visits. For questions 1, 2, 6 and 7, there was no difference in the change in response between the groups over the course of the study. For questions 1, 2, and 6, visit 2 differed significantly from visit 3 and 4. For question 7, visit 2 differed significantly from visit 3, but not 4. Visit 3 did not differ significantly from visit 4 except for question 6. There was no difference in the change in the sum of Q1 through Q5 between the two treatments over the course of the study, but each visit differed significantly from each of the others.

Specifically, the interaction between treatment and visit was not significant ($p = 0.679$), so main effects were analyzed. The main effect for group was not significant ($p = 0.329$), but the main effect for visit was ($p = 0.001$). Thus, there was no difference in change in QOL measured by VAS between the two treatments over the course of the study, but visit 2 differed significantly from Visits 3 and 4, while visit 3 did not differ significantly from Visit 4 ($p = 0.345$).

In summary, there was no significant difference in the change in total QOL (as measured by the VAS) between the two treatment groups over the course of the study. However, both groups improved significantly in QOL relative to baseline at Visits 2, 3, and 4.

## DISCUSSION

Recent clinical trials of treatment for xerostomia have largely failed to provide evidence of new products that increase saliva flow or improve quality of life. Most products for xerostomia relief contain xylitol, which has anti-cariogenic activity. It is not known if xylitol plays a role in saliva output. An open-label, cross-over clinical study on 39 xerostomia patients (without a placebo control) using a product containing olive oil, betaine and xylitol for one week, showed an increase in un-stimulated saliva flow rate [11]. The efficacies of a xylitol-containing chewing gum, a sorbitol-containing lozenge, and a xylitol-containing spray, have each been tested in patients with xerostomia, and none of these products showed marked efficacy in stimulating saliva [12]. This is consistent with the observations from the current study on the placebo lozenge containing 500 mg xylitol. A self-adhering disc containing 500 mg of xylitol was tested in a clinical study with 15 xerostomia subjects, but saliva flow information was not reported [13]. Earlier studies using a maltose-containing lozenge showed a potential benefit for xerostomia [14], but maltose has not been used as a major ingredient in xerostomia products, possibly due to its cariogenic nature.

Malic acid is a naturally occurring compound with a low pH. Clinical trials using a spray containing 1% malic acid reported a modest increase in saliva flow rates [15-17].

There have been a number of clinical trials testing the efficacy of an enzyme-containing product line on xerostomia patients, but the results have not shown efficacy in terms of elevation of saliva flow [18 - 22]. In addition, an enzyme-containing mouthwash failed to lower bacterial

count in a double-blind, crossover clinical trial [22]. In fact, a 1996 human study demonstrated that a mouthwash containing enzymes lowered the salivary pH significantly, without major changes in the microflora or saliva flow [23].

The current study, using a double-blind, placebo-controlled, and randomized study design, demonstrated that after 8 weeks of MTF formula use, there was a statistically significant increase in the un-stimulated saliva flow rate from 0.17 $\pm$ 0.05 ml/5 min to 0.66 $\pm$ 0.24 ml /5 min, an increase of 3.8 fold. Similarly, the stimulated saliva flow rate was increased from 0.65 $\pm$ 0.13 ml/5 min to 1.34 $\pm$ 0.24 ml/5 min, a statistically significant increase of 2.1 fold. To the best of our knowledge, there have been no reports from any clinical trial of a treatment for xerostomia that demonstrated these levels of change in saliva flow rates. Interestingly, significant improvement in both un-stimulated and stimulated saliva output in the intervention group was immediately evident after one week of treatment (Table 4). Therefore, products developed from the MTF formula could provide an objectively effective approach to managing xerostomia. It would be anticipated that the MTF formula would afford an improvement in QOL scores, which are related to the severity of xerostomia. However, both the MTF formula and the active placebo groups showed significant improvements over baseline during the 8 week study, and there was no significant difference between the two groups seen in the questionnaire responses. It remains unclear at this time why there is a discrepancy between the beneficial effect on objective flow rates and subjective QOL measures, although this is consistent with the poor correlation between QOL and saliva flow rates. Longer study periods might reveal differences between treatment and placebo groups either through continued benefit or decline in placebo effect. It is possible that a larger study population would allow an analysis of the relationship between severity of

xerostomia, QOL, and the effect of objective improvement in salivary flow rates on the subjective QOL values.

Importantly, the benefits from this formula are not associated with adverse effects. A determination of whether xerostomia resulting from head and neck cancer therapy (excluded from this study) can be alleviated with this formula is warranted. In addition, cancer patients were not eligible for this study and only a relatively small number of SS patients participated. Therefore trials with cancer patients and a larger SS patient population are needed for a full assessment of the efficacy of the MTF formula. At this time, we do not understand fully the mechanism behind the synergy obtained by the combination of ingredients in this proprietary formulation. Further investigation in animal studies is planned.

In conclusion**,** the natural MighTeaFlow formula resulted in a partial restoration of salivary function in xerostomia patients by significantly increasing both un-stimulated and stimulated saliva flow, relative to the xylitol-containing placebo. Over the 8 week study period, this did not result in an improvement in the QOL greater than the improvement seen in the xylitol-containing placebo group. This formula could provide beneficial outcomes for patients with xerostomia, pending large scale clinical trials and mechanistic studies.

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OTHER INFORMATION

Registration number and name of trial registry

ClinicalTrials.gov Identifier: NCT01647737

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**Table 1**. Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| 1. A complaint of dry mouth as assessed by a response of 30 mm or greater on a Dry Mouth Visual Analog Scale (VAS).<br>2. May have primary or secondary Sjogren's syndrome.<br>3. An unstimulated whole salivary flow rate of $\leq$0.2mL/min.<br>4. Over the age of 18.<br>5. Taking less than three drugs associated with causing xerostomia or salivary gland hypofunction.<br>6. Willing to use natural novel topical dry mouth products.<br>7. Willing to return for all study-associated visits.<br>8. Able to read, understand, and sign the informed consent. | 1. Have received radiation to the head and neck region.<br>2. Unable to read and understand the consent form.<br>3. On greater than three drugs associated with xerostomia or salivary gland hypofunction.<br>4. Require dento-alveolar surgery or extensive dental treatment during the course of the study.<br>5. Require hospitalization for any medical problem during the course of the study.<br>6. Unable to take green tea leaf extract and/or pilocarpus jaborandi leaf extract.<br>7. Uncontrolled medical conditions that require changes in medication during the course of the study.<br>8. Regularly consume green tea and/or components of pilocarpus jaborandi. |

**Table 2.** Visual Analog Scale Form – Xerostomia

Please make a VERTICAL mark on the horizontal line for each question to indicate how you feel today.

Q1. How dry does your mouth feel most of the time?

Dry as a desert 1 ——— 10 Not dry at all

Q2. How comfortable does your mouth feel most of the time?

Uncomfortable 1 ——— 10 Comfortable

Q3. How difficult is it to swallow DRY food without additional liquids?

Very difficult 1 ——— 10 Not difficult

Q4. How difficult is it to swallow ANY food without additional liquids?

Very difficult 1 ——— 10 Not difficult

Q5. How difficult is it for you to speak without drinking liquids?

Very difficult 1 ——— 10 Not difficult

If this is your first evaluation, disregard the following two questions

Q6. Please rate your present condition of dry mouth (xerostomia) compared with your condition at the start of the study. Consider the changes to your dry mouth and other symptoms related to your dry mouth that have occurred since you have started the study.

Worse 1 ——— 10 Improved

Q7. Please rate the overall condition of your dry mouth now compared to how you felt before starting treatment in this study

Worse _____ No Change _____ Better _____

**Table 3**. Patient demographics

| Group | A (intervention) | B (placebo) |
|---|---|---|
| Total number subjects Recruited/enrolled | 30 | 30 |
| Completed study (female) | 25 | 24 |
| Completed study (male) | 1 | 1 |
| Age range | 28-72 | 21-72 |
| Average age | 58.15 ± 11.67 | 59.04 ± 11.36 |
| MSB biopsy focus Score c/w SS | 7 | 3 |
| MSG biopsy focus Score not c/w SS | 19 | 22 |
| Positive smoking history | 5 | 2 |
| Positive alcohol Use history | 13 | 13 |

Sjogren's diagnoses and histologic findings were evaluated using the 2002 classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. A biopsy was determined to be consistent with Sjogren's if there was a focus score of greater than or equal to 2.0.

**Table 4.** Salivary flow rate per 5 min.

| A | SWS Group/n | Week | Mean (ml)/SEM | Change from week 0 | *p* value (vs. week 0) |
|---|---|---|---|---|---|
| | Intervention/30 | 0 | 0.65 ± 0.13 | ---------- | ----- |
| | Intervention /28 | 1 | 0.98 ± 0.22 | 0.35 ± 0.12 | 0.18 |
| | Intervention /27 | 4 | 1.08 ± 0.17 | 0.44 ± 0.16 | 0.04 |
| | Intervention /26 | 8 | 1.34 ± 0.29 | 0.71 ± 0.21 | 0.02 |
| | Placebo/30 | 0 | 0.71 ± 0.20 | ---------- | ----- |
| | Placebo/28 | 1 | 0.92 ± 0.18 | 0.22 ± 0.18 | 0.63 |
| | Placebo/25 | 4 | 0.69 ± 0.13 | -0.03 ± 0.13 | 0.93 |
| | Placebo/25 | 8 | 0.86 ± 0.25 | 0.13 ± 0.12 | 0.65 |

| B | USWS Group/n | Week | Mean (ml)/SEM | Change from week 0 | *p* value (vs. week 0) |
|---|---|---|---|---|---|
| | Intervention /30 | 0 | 0.17 ± 0.05 | ---------- | ----- |
| | Intervention /28 | 1 | 0.56 ± 0.19 | 0.39 ± 0.16 | 0.05 |
| | Intervention /27 | 4 | 0.52 ± 0.12 | 0.35 ± 0.10 | 0.01 |
| | Intervention /26 | 8 | 0.66 ± 0.17 | 0.49 ± 0.15 | 0.01 |
| | Placebo/30 | 0 | 0.40 ± 0.24 | ---------- | ----- |
| | Placebo/28 | 1 | 0.38 ± 0.08 | -0.02 ± 0.08 | 0.89 |
| | Placebo/25 | 4 | 0.37 ± 0.19 | -0.03 ± 0.19 | 0.89 |
| | Placebo/25 | 8 | 0.40 ± 0.20 | 0.00 ± 0.20 | 0.75 |

**Table 5.** Descriptive Statistics at Baseline

| Variable | Group | N | Minimum | Maximum | Mean | Std. Dev. |
|---|---|---|---|---|---|---|
| SWS | Treatment | 30 | 0.0 | 3.4 | 0.65 | 0.73 |
| | Control | 30 | 0.0 | 5.8 | 0.71 | 1.12 |
| UWS | Treatment | 30 | 0.0 | 1.1 | 0.17 | 0.30 |
| | Control | 30 | 0.0 | 7.0 | 0.40 | 1.32 |
| Q1 | Treatment | 30 | 1.0 | 92.0 | 23.37 | 18.83 |
| | Control | 30 | 0.0 | 81.0 | 24.07 | 21.65 |
| Q2 | Treatment | 30 | 0.0 | 103.0 | 26.67 | 23.56 |
| | Control | 30 | 0.0 | 58.0 | 18.70 | 15.67 |
| Q3 | Treatment | 30 | 0.0 | 96.0 | 15.73 | 20.73 |
| | Control | 30 | 0.0 | 87.0 | 21.03 | 23.92 |
| Q4 | Treatment | 30 | 1.0 | 106.0 | 28.37 | 27.36 |
| | Control | 30 | 0.0 | 88.0 | 33.57 | 26.01 |
| Q5 | Treatment | 30 | 0.0 | 106.0 | 30.10 | 27.95 |
| | Control | 30 | 0.0 | 98.0 | 34.60 | 29.38 |
| Q1-Q5 | Treatment | 30 | 10.0 | 504.0 | 124.23 | 101.34 |
| | Control | 30 | 0.0 | 339.0 | 131.93 | 87.66 |
| QOL | Treatment | 30 | 12.0 | 51.0 | 31.93 | 11.19 |
| | Control | 30 | 13.0 | 60.0 | 31.57 | 12.00 |

**Table 6.** Descriptive Statistics for Change from Baseline for Outcome Variables

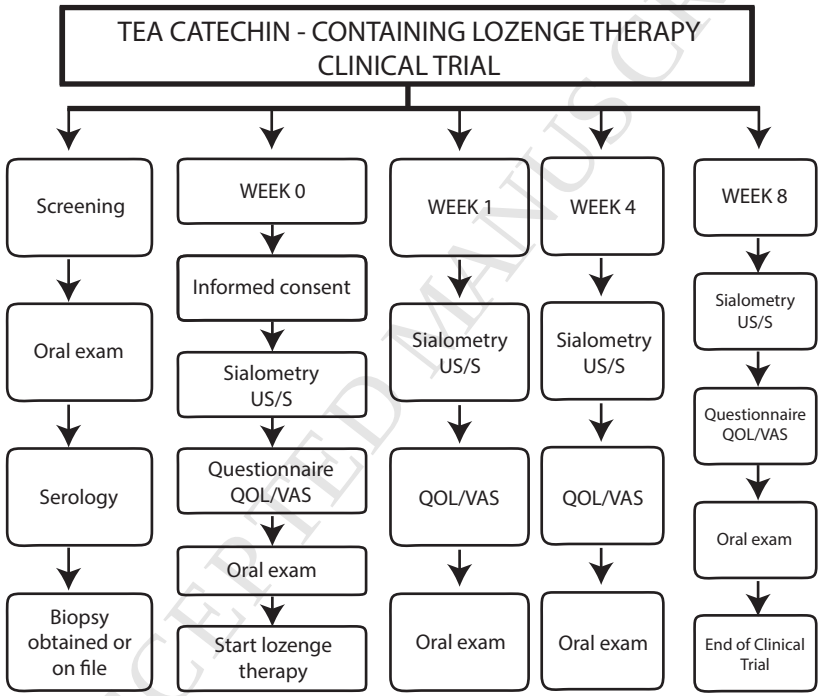
| Variable | Group | Visit Number | N | Minimum | Maximum | Mean | Std. Dev. |
|---|---|---|---|---|---|---|---|
| SWS | Treatment | 2 | 28 | -0.89 | 1.94 | 0.35 | 0.64 |
| | Treatment | 3 | 27 | -2.05 | 1.85 | 0.44 | 0.83 |
| | Treatment | 4 | 25 | -0.69 | 3.71 | 0.71 | 1.05 |
| | Control | 2 | 28 | -0.61 | 4.68 | 0.22 | 0.93 |
| | Control | 3 | 25 | -2.31 | 0.74 | -0.03 | 0.65 |
| | Control | 4 | 25 | -1.52 | 1.83 | 0.13 | 0.62 |
| UWS | Treatment | 2 | 28 | -0.15 | 3.00 | 0.41 | 0.83 |
| | Treatment | 3 | 27 | -0.30 | 1.70 | 0.37 | 0.54 |
| | Treatment | 4 | 26 | -0.70 | 2.94 | 0.49 | 0.74 |
| | Control | 2 | 28 | -1.51 | 1.29 | 0.02 | 0.42 |
| | Control | 3 | 25 | -4.00 | 2.15 | -0.03 | 0.94 |
| | Control | 4 | 25 | -4.30 | 1.92 | 0.00 | 1.00 |
| Q1 | Treatment | 2 | 28 | -30.00 | 53.00 | 9.18 | 17.73 |
| | Treatment | 3 | 27 | -8.00 | 78.00 | 18.93 | 22.69 |
| | Treatment | 4 | 26 | -6.00 | 67.00 | 25.50 | 21.41 |
| | Control | 2 | 28 | -78.00 | 54.00 | 1.54 | 22.99 |
| | Control | 3 | 25 | -49.00 | 63.00 | 11.96 | 24.70 |
| | Control | 4 | 25 | -77.00 | 66.00 | 16.40 | 30.23 |
| Q2 | Treatment | 2 | 28 | -24.00 | 39.00 | 5.07 | 12.49 |
| | Treatment | 3 | 27 | -14.00 | 56.00 | 13.41 | 20.54 |
| | Treatment | 4 | 26 | -6.00 | 68.00 | 20.04 | 19.12 |
| | Control | 2 | 28 | -26.00 | 57.00 | 7.21 | 16.85 |
| | Control | 3 | 25 | -12.00 | 62.00 | 17.72 | 19.09 |
| | Control | 4 | 25 | -19.00 | 88.00 | 24.32 | 26.16 |

**Table 7.** Descriptive Statistics for Q6

| Group | Visit Number | N | Minimum | Maximum | Mean | Std. Dev. |
|---|---|---|---|---|---|---|
| Treatment | 2 | 28 | 1.00 | 73.00 | 41.57 | 19.50 |
| Treatment | 3 | 27 | 11.00 | 91.00 | 50.37 | 20.68 |
| Treatment | 4 | 26 | 3.00 | 103.00 | 59.81 | 26.45 |
| Control | 2 | 28 | 4.00 | 71.00 | 39.14 | 17.84 |
| Control | 3 | 25 | 0.00 | 78.00 | 48.44 | 19.21 |
| Control | 4 | 25 | 16.00 | 102.00 | 56.88 | 24.13 |

**Table 8.** Summary od Data for Q7

| Group | Visit Number | N | Worse (Pet) | No Change (Pet) | Better (Pet) |
|---|---|---|---|---|---|
| Treatment | 2 | 28 | 10.7 | 50.00 | 39.3 |
| Treatment | 3 | 27 | 3.7 | 25.9 | 70.4 |
| Treatment | 4 | 26 | 3.9 | 23.1 | 73.1 |
| Control | 2 | 28 | 7.1 | 57.1 | 35.7 |
| Control | 3 | 25 | 8.0 | 24.0 | 68.0 |
| Control | 4 | 25 | 4.0 | 32.0 | 64.0 |



Quality of Life and Statistical Analyses

Summary statistics for the baseline values for Q1-Q5 are presented in Table 5. (The Q6 and Q7 outcomes were not assessed at baseline). Summary statistics for the change from baseline for each group at each visit for each outcome except Q6 and Q7 are presented in Table 6. The Shapiro-Wilk test indicated that the assumption of normality was violated for the change scores for SWS, UWS, Q1, Q3, Q5, Q1-Q5, and QOL, so rank-based statistical methods were used for each of these outcomes. Normal theory methods were used for Q2 and Q4. Summary statistics for Q6 for each group at each visit are presented in Table 7. The Shapiro-Wilk test indicated that the assumption of normality was violated for Q6, so rank-based statistical methods were used. The data for Q7 are summarized by category for each group at each visit in Table 8.

Q1. How dry does your mouth feel most of the time?

In the rank-based repeated measures analysis for change in Q1, the interaction between treatment and visit was not significant ($p = 0.952$), so main effects were analyzed. The main effect for group was not significant ($p = 0.131$), but the main effect for visit was ($p < 0.001$). The repeated measures version of the Tukey-Kramer method showed that Visit 2 differed significantly from both Visit 3 ($p = 0.011$) and Visit 4 ($p < 0.001$), but Visit 3 did not differ significantly from Visit 4 ($p = 0.095$). Thus, there was no difference in change in Q1 between the two treatments over the course of the study, but Visit 2 differed significantly from Visits 3 and 4.

Q2. How comfortable does your mouth feel most of the time?

In the repeated measures analysis for change in Q2, the interaction between treatment and visit was not significant ($p = 0.936$), so main effects were analyzed. The main effect for group was not significant ($p = 0. 323$), but the main effect for visit was ($p < 0.001$). The repeated measures

version of the Tukey-Kramer method showed that Visit 2 differed significantly from both Visit 3 ($p = 0.011$) and Visit 4 ($p < 0.001$), but Visit 3 did not differ significantly from Visit 4 ($p = 0.094$). Thus, there was no difference in change in Q2 between the two treatments over the course of the study, but Visit 2 differed significantly from Visits 3 and 4.

Q3. How difficult is it to swallow DRY food without additional liquids?

In the rank-based repeated measures analysis for the change in Q3, the interaction between treatment and visit was not significant ($p = 0.575$), so main effects were analyzed. Neither the main effect for group ($p = 0.344$), nor the main effect for visit were statistically significant ($p = 0.056$). Thus, there was no difference in change in Q3 between the two treatments over the course of the study, nor did Visits 2, 3, and 4 differ from each other.

Q4. How difficult is it to swallow ANY food without additional liquids?

In the repeated measures analysis for the change in Q4, the interaction between treatment and visit was not significant ($p = 0.820$), so main effects were analyzed. Neither the main effect for group ($p = 0.127$), nor the main effect for visit were statistically significant ($p = 0.071$). Thus, there was no difference in change in Q4 between the two treatments over the course of the study, nor did Visits 2, 3, and 4 differ from each other.

Q5. How difficult is it for you to speak without drinking liquids?

In the rank-based repeated measures analysis for the change in Q5, the interaction between treatment and visit was not significant ($p = 0.809$), so main effects were analyzed. Neither the main effect for group ($p = 0.064$), nor the main effect for visit were statistically significant ($p =$

0.189). Thus, there was no difference in change in Q5 between the two treatments over the course of the study, nor did Visits 2, 3, and 4 differ from each other.

Sum of Q1 through Q5

In the rank-based repeated measures analysis for the change in Q1-Q5, the interaction between treatment and visit was not significant ($p = 0.994$), so main effects were analyzed. The main effect for group was not significant ($p = 0.068$), but the main effect for visit was ($p < 0.001$). The repeated measures version of the Tukey-Kramer method showed that Visit 2 differed significantly from both Visit 3 ($p = 0.031$) and Visit 4 ($p < 0.001$), and Visit 3 differed significantly from Visit 4 ($p = 0.036$). Thus, there was no difference in the change in the sum of Q1 through Q5 between the two treatments over the course of the study, but each visit differed significantly from each of the others.

Q6. Please rate your present condition of dry mouth (xerostomia) compared with your condition at the start of the study. Consider the changes to your dry mouth and other symptoms related to your dry mouth that have occurred since you have started the study.

In the rank-based repeated measures analysis for Q6, the interaction between treatment and visit was not significant ($p = 0.986$), so main effects were analyzed. The main effect for group was not significant ($p = 0.556$), but the main effect for visit was ($p < 0.001$). The repeated measures version of the Tukey-Kramer method showed that Visit 2 differed significantly from both Visit 3 ($p = 0.020$) and Visit 4 ($p < 0.001$), and Visit 3 differed significantly from Visit 4 ($p = 0.005$).

Thus, there was no difference in Q6 between the two treatments over the course of the study, but each visit differed significantly from each of the others.

Q7. Please rate the overall condition of your dry mouth now compared to how you felt before starting treatment in this study.

In the GEE-based repeated measures analysis for Q7, the interaction between treatment and visit was not significant ($p = 0.613$), so main effects were analyzed. The main effect for group was not significant ($p = 0.746$), but the main effect for visit was ($p = 0.004$). Pairwise comparisions using a GEE model with Bonferroni-adjusted significance level of 0.017 showed that Visit 2 differed significantly from Visit 3 ($p = 0.003$), but not from Visit 4 ($p = 0.043$). In addition, Visit 3 did not differ significantly from Visit 4 ($p = 0.838$). Thus, there was no difference in Q7 between the two treatments over the course of the study, but Visit 2 differed significantly from Visit 3.

QOL as measured by VAS

In the rank-based repeated measures analysis for the change in QOL (as measured by the VAS), the interaction between treatment and visit was not significant ($p = 0.679$), so main effects were analyzed. The main effect for group was not significant ($p = 0.329$), but the main effect for visit was ($p = 0.001$). The Tukey-Kramer method for repeated measures showed that Visit 2 differed significantly from both Visit 3 and Visit 4 ($p = 0.002$ for both comparisons), but Visit 3 did not differ significantly from Visit 4 ($p = 0.345$). Thus, there was no difference in change in QOL between the two treatments over the course of the study, but Visit 2 differed significantly from Visits 3 and 4.

# Statement of Clinical Relevance

Therapy using a proprietary formula containing tea catechins showed significant increases in un-stimulated and stimulated saliva flow after 8 weeks of trial. This novel finding could significantly enhance the oral health and quality of life in populations suffering from xerostomia.