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Acupuncture-like Transcutaneous Electrical Nerve Stimulation versus Pilocarpine in Treating Radiation-Induced Xerostomia: Results of RTOG 0537 Phase 3 Study

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Abstract

Purpose and Objectives—This report presents the analysis of the RTOG 0537 multi-center randomized study that compared acupuncture-like transcutaneous stimulation (ALTENS) to pilocarpine (PC) for relieving radiation-induced xerostomia (RIX).

Methods and Materials—Eligible patients were randomized to twice weekly 20 minute ALTENS sessions for 24 sessions over 12 weeks or PC (5mg, 3 times daily for 12 weeks). The primary endpoint was the change in the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) scores from baseline to 9 months from randomization (mfr). Secondary endpoints included basal and citric acid primed whole salivary production (WSP), ratios of positive responders (defined as patients with ≥ 20% reduction in overall RIX symptom burden), and the presence of adverse events based on CTCAE v.3. An intention-to-treat analysis was conducted.

Results—148 patients were randomized. Only 96 patients completed the required XeQOLS and were evaluable at 9 mfr (representing merely 68.6% statistical power). Seventy-six patients were evaluable at 15 mfr. The median change in the overall XeQOLS in ALTENS/PC groups at 9 and 15 mfr were −0.53/−0.27 (P=0.45) and −0.6/−0.47 (P=0.21). The corresponding percentages of positive responders were 81%/72% (P=0.34) and 83%/63% (P=0.04). Changes in WSP were not significantly different between the groups. Grade 3 or less adverse events, mostly consisting of Grade 1, developed in 20.8% of patients in the ALTENS group and in 61.6% of the PC group.

Conclusions—The observed effect size was smaller than hypothesized and statistical power was limited, since only 96 of the recruited 148 patients were evaluable. The primary endpoint -- the change in RIX symptom burden at 9 mfr, was not significantly different between the ALTENS and PC groups. There was significantly less toxicity in patients receiving ALTENS.

INTRODUCTION

Current management for radiation-induced xerostomia is symptomatic relief and prevention of oral and dental problems. Cholinergic agonists provide minimal sustained benefit and can have significant adverse effects[1-3].

Acupuncture-like transcutaneous nerve stimulation (ALTENS) was suggested by a previous non-randomized phase 2 trial to be a potential treatment alternative for radiation-induced xerostomia[4]. Based on this trial, a multi-center randomized controlled phase 2/3 study comparing oral pilocarpine, the current standard treatment, with ALTENS was conducted by the Radiation Therapy Oncology Group (RTOG). The phase 2 results of this RTOG study demonstrated the feasibility in delivering ALTENS in a multi-center trial settings and a beneficial treatment response. ALTENS treatments were well tolerated by patients with few adverse effects[5]. This report presents the phase 3 results of this study.

METHODS

Objectives

The primary study objective was to determine whether ALTENS would reduce the overall radiation-induced xerostomia burden compared to oral pilocarpine. The primary endpoint

was the change in overall xerostomia burden, measured by the University of Michigan Xerostomia Related Quality of Life Scale (XeQOLS) at 9 months from randomization. The following secondary objectives were studied to compare the differences in:

- percentages of positive responder, defined as patient who had at least a 20% improvement from baseline XeQOLS
- stimulated (citric acid primed) and basal whole salivary production (WSP)
- percentages of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 criteria
- change in overall xerostomia burden and
- change in overall quality of life measured by the University of Washington Head and Neck Symptom Score (UWHNSS).

Patient Population

Eligible patients were at least 18 years old who had completed radiation (intensity modulated, IMRT or standard) with or without chemotherapy 3 months to 2 years before study entry and without evidence of recurrence. Patients who were disease free from other malignancies for at least 3 years prior to study entry were still eligible. Patients must have reported grade 1 or higher xerostomia (CTCAE v3.0) with a residual basal WSP > 0.1 ml per minute. Patients must have 0 to 2 Zubrod performance status. Patients who had received pilocarpine or cevimeline previously were strictly required to discontinue these medications at least 2 weeks prior to randomization. All patients provided study-specific consents. Patients with contraindications to pilocarpine or ALTENS were excluded. Specified contraindications include unstable cardiac disease, pacemaker in-situ, chronic obstructive pulmonary disease, respiratory illness requiring hospitalization, acute bacterial or fungal infection requiring intravenous treatments and pregnancy.

Study Design

A prospective randomized controlled design was utilized. Patients were stratified according to prior pilocarpine treatment and time after radiation therapy and/or chemotherapy. Zelen's treatment allocation scheme was used to balance patient factors other than institutions[6]. Within each stratum, patients were randomized in a 1:1 ratio to either ALTENS or pilocarpine treatment.

Treatment Interventions—ALTENS were administered with a Codetron™ (model 902-C, EHM Rehabilitation Technologies Ltd., Ontario, Canada) TENS units and Karaya electrode pads. Bilateral acupuncture points: SP6, ST36, LI4 using uncommon electrodes and CV24 using the common electrode were stimulated[4,5]. Sequences of 250 millisecond square pulses with a 4 Hz repetition rate were delivered. Each acupuncture point, except CV24, was stimulated for 10 seconds at a time. CV24, the site for the common electrode, was stimulated throughout the treatment session. Stimulation intensity (between level 3 to 6 on the machine) was adjusted to produce a deep strong aching sensation at each acupuncture point. Random switching among electrodes enabled by the Codetron™ embedded random circuit was employed to prevent brain habituation to stimulation[7]. ALTENS was started

within 14 days after study enrollment. All patients were to receive 24 ALTENS sessions (20 minutes each, two sessions per week), over 12 weeks. Two weeks without treatment were allowed and all outstanding sessions were administered in the remainder of the 12 week period, not to exceed three sessions per week. All treatments were delivered at RTOG participating academic and community-based institutions. Staff administering the ALTENS received training at RTOG meetings. Slides of training materials and a training video were posted on the RTOG website. For each patient, photographs of electrode pad positions on the acupuncture points were sent electronically to the principal investigator for rapid approval before the third treatment session.

Pilocarpine treatment started within 14 days of enrollment. Patients received 5 mg pilocarpine orally three times daily for 12 weeks and then stopped for the rest of the study. There was no make-up for missed dose. Dose modification was permitted due to pilocarpne intolerance. Patients completed drug diaries and returned all medications for counting to determine treatment compliance.

Study Endpoint Assessments—All endpoint assessments were conducted at baseline and at 4, 6, 9 and 15 months after the date of randomization.

The XeQOLS is a validated patient reported 15 items assessment scale with four domains — physical functioning, pain/discomfort, personal/psychological functioning and social functioning. The score is the average of all responses of all domains and could range from 0 to 4.Higher scores indicate increased xerostomia burden. This scale has high reproducibility and sensitivity[8-12].

Positive treatment responders were defined as patients who had at least a 20% improvement from the baseline XeQOLS scores, similar to that reported in previous randomized trials involving pilocarpine[13-15].

The UWHNSS is a patient reported questionnaire designed specifically to address problems incurred by head and neck cancer patients[16].The results will be reported in another manuscript.

Whole salivary production (WSP) was measured by the expectoration weight. One gram of saliva produced was considered as 1 ml of saliva.

For basal WSP, before each assessment, patients were required to refrain from eating, drinking, and smoking for at least one and a half hours. Patients then expectorated continuously into a pre-weighted dry container for five minutes without swallowing. The collected saliva with the container was weighted (total weight) immediately after each collection. The difference between the total weight and the container weight was considered equal to the volume of saliva produced. WSP was expressed in ml/min calculated by dividing the measured volume by 5.

For stimulated WSP, patients were given 5 ml of 2% citric acid solution to rinse in the mouth for 15 seconds and then completely expectorated the citric acid followed by the measurement procedure as described above.

Statistics—No data were available to hypothesize the difference in the mean change of XeQOLS scores at 9 months from randomization, the primary endpoint, between the two treatment groups. An effect size of 0.50 was chosen for sample size calculation since the study team thought that a positive study with such magnitude of change would be more persuasive to implement the use of ALTENS. Based on a two-sided t-test with alpha=0.05 and one interim analysis, 130 patients were required for 80% statistical power. Adjusting by 10% for lost to follow-up and retrospective ineligibility of recruited subjects yielded a sample size of 144 patients. Intention-to-treat analysis was conducted. Missing scores were imputed by taking the average score of completed items and extending it across all items.For all alive patients at 9 months, missing baseline and 9 month assessments were imputed using Markov chain Monte Carlo multiple imputation. Treatment was tested using analysis of covariance along with the stratification variables and the baseline XeQOLS scores. Treatment groups were compared by Wilcoxon rank-sum test due to the non-normality of the data. Differences between groups in adverse events were tested using a Chi-Square test. The effects of pre-treatment characteristics, treatment group and stratification factors on the overall XeQOLS score across time were examined using a general linear model.

RESULTS

148 patients (73 in pilocarpine group and 75 in ALTENS group) were enrolled from August, 2010 to December, 2011. In the ALTENS group, two patients were ineligible for either having the physical examination/history conducted or prior chemotherapy completed outside the required 8-week period before enrolment. The pre-treatment characteristics are shown in Table 1. There were no significant differences between the two groups. Using a general linear model, apart from prior usage of chemotherapy (estimate = −0.35, SE = 0.18, $p<0.05$), there were no pre-treatment characteristics that significantly correlated with the overall XeQOLS scores across all time points.

In the ALTENS group 93% of patients completed greater than 85% of the protocol-specified treatments compared to 73% in the pilocarpine group. Patient refusal (16%) was the main reason for non-compliance in the pilocarpine group.

For the endpoints analysis, there were only 96 and 76 patients evaluable with all items completed at 9 and 15 months from randomization, respectively. This represents 68.6% statistical power for detecting an effect size of 0.50 or larger in the primary endpoint between the two groups. All time points saw a higher compliance rate in completing the assessments in the ALTENS group. The largest factor contributing to patient non-compliance was consent withdrawal. At 9 months from randomization, 15 patients withdrew their consent including 11 in the pilocarpine group. Sixteen patients either did not complete the baseline form (5) or the XeQOLS before treatment (11). Nineteen patients, 13 in the pilocarpine group, failed to complete XeQOLS or completed the scale outside the planned time frame. These alive patients were included in the imputation analysis for the primary endpoint.

In these 96 evaluable patients, the mean baseline overall XeQOLS scores of the pilocarpine group (1.7) was slightly higher, indicating a poorer baseline quality of life, than that of the

ALTENS group (1.5), p=0.047. Patients previously treated with pilocarpine had a 0.46 loweroverall mean score, suggesting less baseline xerostomia burden, compared to patients not previously treated with pilocarpine (p=0.014). White patients experienced an overall mean score that was 0.61 higher than non-white patients, indicating worse xerostomia burden (p=0.002).

The baseline scores were subtracted from the follow-up scores and so a negative change score indicated an improvement of the xerostomia burden. Table 2 shows the results of the change in overall XeQOLS scores for the 96 evaluable patients. There was no statistical significance between the two groups for the primary endpoint at 9 months from randomization (p=0.45). For all follow-up time points, the median change scores in the ALTENS group were consistently improved compared to that of the pilocarpine group, but none reached statistical significance. The median change in overall XeQOLS scores in ALTENS/pilocarpine groups were −0.47/−0.27 (P=0.11), −0.4/−0.33 (P=0.31), −0.53/−0.27 (P=0.45), −0.6/−0.47 (P=0.21) at 4, 6, 9, 15 months from randomization. There were also no statistical significant differences in the change in XeQOLS domain scores.

Analysis of data including imputed item scores revealed, contrary to the results of the complete data, no significant difference in overall baseline XeQOLS score (p=0.12) between the two study groups. The only significant difference was seen in the change in the overall score at 4 months in favor of the ALTENS group (median change score for ALTENS/ pilocarpine: −0.47/−0.26, (p=0.037). There were, however, no other significant differences between the two groups in the change in overall score or the change in domain scores.

Treatment response rates between the two study groups are shown in Table 3. There were consistently more positive responders in the ALTENS groups at each time point. At 4, 6, 9 and 15 months from randomization, the percentages of positive responders in the ALTENS and pilocarpine groups, were 65.4% versus 48.8%, 66% versus 57.8%, 81.1% versus 72.1% and 83% versus 62.8%, respectively. The response rate was significant at 15 months from randomization (p=0.035) but was not significant at the other time points.

Adverse events are shown in Table 4. There were two grade 3 events in the pilocarpine group (dry mouth and blurred vision) and one in the ALTENS group (headache). Overall, 61.6% of patients in the pilocarpine group, had grade 3 or less non-hematologic adverse events compared to 20.9% in the ALTENS group. There were no significant differences between the groups with respect to the highest grade of adverse events related to treatment and/or those with any relation to treatment at 9 months from randomization (p=0.51 and 0.67 respectively).

Basal and stimulated whole salivary production data are shown in table 5 and 6 respectively. There were no significant differences in the change in whole salivary production between the two groups at any of the time points.

DISCUSSION

This study compared ALTENS, a non-invasive treatment with a low toxicity profile, to the current treatment standard, oral pilocarpine which often has side effects that decrease

tolerability. This study showed no statistically significant difference in the pre-defined study endpoint—the change of XeOOLS scores at 9 months from randomization. However, in the ALTENS group, there was a consistent trend towards greater improvement in XeQOLS scores at all follow-up time points and a statistically significant higher response rate at 15 months from randomization.

The large percentage of patients, particularly in the pilocarpine group, who failed to complete the planned assessments and baseline information was unexpected. We suspected that it was the failure of the research team in some participating centers to ensure completion of assessments. This lost of evaluable patients could not be adequately compensated by the 10% adjustment, adopted based on a previous pilocarpine trial, in calculating the study sample size[15]. Only 96 out of the 146 eligible patients recruited were evaluable for the primary endpoint, reducing the study statistical power to 68.6% in detecting the pre-defined effect size of 0.5 or greater between the groups. This limits the generalizability of this trial. Given that the mean (but not the median) changes in the XeQOLS scores were the same in both treatment groups for the primary endpoint, the observed difference in effect size was actually zero implying that ALTENS is not superior or inferior to oral pilocarpine in the primary treatment outcome.

Unfortunately, we did not collect data regarding the reasons for consent withdrawals. In this type of trial involving new treatment approach, we postulated that the main reason for consent withdrawals was that patients weren't randomized to the arm they wanted. This was reflected in the higher proportion of consent withdrawals in the pilocarpine arm than the ALTENS arm.

The higher baseline xerostomia burden in the pilocarpine group could perhaps have affected the observed pilocarpine treatment outcome. However, there was no correlation of baseline xerostomia burden with the efficacy of pilocarpine treatment. Analysis using the general linear model also failed to show, apart from prior chemotherapy, any pre-treatment characteristics that significantly correlated with the overall XeQOLS scores across all time points. Moreover, analysis of the data including the imputed items failed to show any difference in the baseline xerostomia burden between the pilocarpine and ALTENs groups. This implies that analysis of a more complete data set will likely show insignificant difference between the two groups.

A major drawback in our study design was that radiation treatment details were not collected. We presumed that well-defined eligibility criteria would provide adequate patient screening of patients; that parotid sparing IMRT would be the standard radiation technique for head and neck cancers during the study period and that randomization would balance the patient characteristics in both groups. However, these assumptions are unlikely to adequately account for all the factors, for example, mean doses to parotid, submandibular glands and oral mucosa; primary tumor anatomical sub-sites and radiation techniques, that are known to be predictive of long-term xerostomia. This drawback can make interpretation of the study findings difficult.

The choice to examine ALTENS was mainly supported by the observed positive treatment response for radiation-induced xerostomia in a non-randomized phase 2 trial[4].Its low toxicity profile shown in other trials also makes it an attractive non-invasive treatment option[17]. In addition, the high treatment compliance rate, the ease of applying and standardizing ALTENS treatment ensure its feasibility in existing clinical settings and in multi-center trials[5]. However, because ALTENS requires the induction of tolerable dull aching sensation in patients, placebo controlled trial with sham ALTENS will be impractical.

In this study, the primary endpoint was assessed at 9 months from randomization, (6 months after completing the intervention). This time delay in endpoint assessment was to test the hypothesis that salivary gland tissue may regenerate after ALTENS treatment. This hypothesis was based on the demonstrated salivary gland tissue regeneration after electrical stimulation in an animal study and the sustained response after ALTENS (unpublished results from xxx University) or acupuncture seen in previous clinical trials[18, 19]. There is no evidence that pilocarpine can stimulate tissue regeneration. Another reason for the time delay in endpoint assessment was to minimize the possibility of losing patients to follow-up. The secondary time point at 15 months from randomization was established to capture a sustained response between the two groups. There was a trend consistently towards a greater favorable median change in XeQOLS scores in the ALTENS group. Nevertheless, xerostomia burden can gradually improve after radiation treatment, and the observed improvement in XeQOLS scores in both groups can also be explained by the natural history of parotid sparing IMRT. Salivary gland functional recovery has been observed for up to 36 months after radiation treatment and mostly within the first 12 month follow-up[20, 21]. Inclusion of patients who still had residual salivary function and who were at 3 months to 2 years after their radiation treatment was to capture the window of salivary gland recovery that may be augmented by the hypothesized salivary tissue regeneration by ALTENS.

To be consistent with previous studies that have utilized predefined response rate as primary endpoint, the percentage of positive treatment responders, defined as patients who had at least 20% improvement from baseline XeQOLS scores, was also evaluated[14-16]. Interestingly, there were higher percentages of positive responders in the ALTENS group at all time points. These group differences reached statistically significance at 15 months from randomization. However, this improvement may solely be due to attrition between 9 and 15 months in the pilocarpine group.

There was no significant difference observed in whole salivary production between the two study groups despite a trend toward improvement in the XeQOLS scores existed in the ALTENS group. This discrepancy could be explained by the consistently observed weak correlation or lack of correlation of salivary flow and patient reported outcome assessment tools[14, 22].

The study methodology demanded equal intervention periods in both two groups. Pilocarpine was used at a predefined dose for only 12 weeks and was discontinued. This treatment schedule is not standard clinical practice. Usually pilocarpine treatment is maintained until lack of efficacy or intolerance occurs. The observed better response rates in

the ALTENS group may not have been apparent if such maintenance pilocarpine treatment had been utilized. However, more patients in the pilocarpine group would have likely suffered from treatment intolerance. There were three times more patients in the pilocarpine group with grade 3 or less treatment related toxicities compared to the ALTENS group. The low toxicity profile of ALTENS observed was similar to that seen in the phase 2 portion of this study and other clinical studies using ALTENS[5, 17]. Conversely, a maintenance strategy with ALTENS may have resulted in significant xerostomia improvement in the ALTENS group with possibly less severe toxicity and better treatment tolerance.

This study has demonstrated that standardized ALTENS could be conducted in a randomized multi-center trial setting. Because of the insufficient number of evaluable patients, the insignificant differences in xerostomia burden detected between the two groups may have resulted from the substantial reduction in the study statistical power that led to a failure to detect the pre-defined degree of differences between the two groups. Thus, the study could not determine if the efficacy of ALTENS is inferior or superior compared to that of pilocarpine in reducing radiation-induced xerostomia. In view of the findings that there was a consistent trend of higher response rates in patients received ALTENS and that the response rate reached statistical significance at around a year after treatment completion, further studies, with ALTENS given for a longer treatment period and response rate assessments conducted with longer follow up, may be worthwhile to adequately explore the potential effectiveness of ALTENS in managing this debilitating condition.

CONCLUSIONS

The primary endpoint of the change of radiation-induced xerostomia symptom burden at 9 months from randomization was not shown to be significantly different between the ALTENS and the pilocarpine groups. There was significantly less toxicity in patients receiving ALTENS. This trial was insufficient to determine the potential efficacy of ALTENS compared to that of pilocarpine.

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Table 1

Patients Pre-treatment Characteristics

	Pilocarpine (n=73)	ALTENS (n=73)	P-value[§]
Age (years)			
Median	59	58	0.83[†]
Min - Max	29 - 78	42 - 83	
Q1 - Q3	53 - 63	53 - 65	
Gender			
Male	63 (86.3%)	62 (84.9%)	0.81
Female	10 (13.7%)	11 (15.1%)	
Race			
American Indian or Alaska Native	1 (1.4%)	2 (2.7%)	n/a
Asian	5 (6.8%)	4 (5.5%)	
Black or African American	5 (6.8%)	2 (2.7%)	
Native Hawaiian or other Pacific Islander	1 (1.4%)	0 (0.0%)	
White	61 (83.6%)	65 (89.0%)	
Ethnicity			
Hispanic or Latino	6 (8.2%)	2 (2.7%)	n/a
Not Hispanic or Latino	62 (84.9%)	69 (94.5%)	
Unknown	5 (6.8%)	2 (2.7%)	
Zubrod Performance Status			
0	58 (79.5%)	60 (82.2%)	n/a
1	15 (20.5%)	12 (16.4%)	
2	0 (0.0%)	1 (1.4%)	
Country of Residence			
United States	51 (69.9%)	51 (69.9%)	0.99
Canada	22 (30.1%)	22 (30.1%)	
Prior Chemotherapy			
No	16 (21.9%)	15 (20.5%)	0.84
Yes	57 (78.1%)	58 (79.5%)	
Time since RT +/− Chemotherapy[*]			
3-6 months ago	19 (26.0%)	19 (26.0%)	0.93
More than 6 months to 1 year ago	28 (38.4%)	30 (41.1%)	
1-2 years ago	26 (35.6%)	24 (32.9%)	

	Pilocarpine (n=73)	ALTENS (n=73)	P-value[§]
Prior Use of Pilocarpine[*]			
No	63 (86.3%)	62 (84.9%)	0.81
Yes	10 (13.7%)	11 (15.1%)	

Q1 = first quartile; Q3 = third quartile.

[*] Stratification factor;

[§] P-value from Chi-square test

[†] P-value from two-sided Wilcoxon signed rank test with normal approximation

Table 2

Changes in overall XeQOLS at 4, 6, 9 and 15 months from randomization

	Pilocarpine	ALTENS	P-value[§]
Overall Score (4 months)	(n=43)	(n=52)	
Mean	−0.30	−0.40	0.11
Std. Dev.	0.60	0.70	
Median	−0.27	−0.47	
Min - Max	−2.3 to − 0.87	−2.3 to − 1.6	
Q1 - Q3	−0.60 to 0	−0.80 to −0.13	
Overall Score (6 months)	(n=45)	(n=47)	
Mean	−0.40	−0.50	0.31
Std. Dev.	0.70	0.70	
Median	−0.33	−0.40	
Min - Max	−2.3 to −1.0	−2.2 to −1.1	
Q1 - Q3	−0.73 to −0.20	−0.87 to −0.14	
Overall Score (9 months)	(n=43)	(n=53)	
Mean	−0.50	−0.50	0.45
Std. Dev.	0.80	0.70	
Median	−0.27	−0.53	
Min - Max	−2.6 to −0.80	−2.1 to −1.47	
Q1 - Q3	−1.1 to −0	−0.87 to −0.20	
Overall Score (15 months)	(n=35)	(n=41)	
Mean	−0.50	−0.60	0.21
Std. Dev.	0.60	0.60	
Median	−0.47	−0.60	
Min - Max	−2.3 to − 1	−1.7to −1.3	
Q1 - Q3	−0.87 to 0.11	−1.0 to −0.20	

Q1 = first quartile; Q3 = third quartile.

[§]P-value from Wilcoxon rank sum test using t approximation

Table 3

Treatment Response Rates between the Pilocarpine and ALTENS group

	Pilocarpine	ALTENS	P-value[§]
Response at 4 Months	(n=43)	(n=52)	
Non-Responder	22 (51.2%)	18 (34.6%)	0.14
Responder	21 (48.8%)	34 (65.4%)	
Response at 6 Months	(n=45)	(n=47)	
Non-Responder	19 (42.2%)	16 (34.0%)	0.52
Responder	26 (57.8%)	31 (66.0%)	
Response at 9 Months	(n=43)	(n=53)	
Non-Responder	12 (27.9%)	10 (18.9%)	0.34
Responder	31 (72.1%)	43 (81.1%)	
Response at 15 Months	(n=35)	(n=41)	
Non-Responder	16 (37.2%)	8 (17.0%)	0.04
Responder	27 (62.8%)	39 (83.0%)	

Responder:≥ 20% reduction (improvement) in XeQOLS score from baseline

[§]P-value from Fisher's Exact Test

Table 4

Summary of worst non-hematological adverse events that were definitely, probably or possibly related to treatment in the pilocarpine and the ALTENS groups.

Grade	Pilocarpine (n=73)	ALTENS (n=72)
1	24 (32.9%)	12 (16.7%)
2	19 (26.0%)	2 (2.8%)
3	2 (2.7%)	1 (1.4%)
4	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)

Table 5

Basal Whole Salivary Production of Study Groups

	Pilocarpine	ALTENS	P-value[§]
Baseline	(n=70)	(n=73)	
Mean	1.2	1.2	0.85
Std. Dev.	1.0	0.7	
Median	1.0	1.0	
Min - Max	0.10 - 5.1	0.10 - 3.4	
Q1 - Q3	0.60 - 1.5	0.70 - 1.5	
4 Months	(n=49)	(n=63)	
Mean	1.2	1.3	0.39
Std. Dev.	1.1	1.0	
Median	1.0	1.0	
Min - Max	0 - 5.5	0 - 4.1	
Q1 - Q3	0.50 - 1.3	0.51 – 2.0	
6 Months	(n=47)	(n=58)	
Mean	1.3	1.3	0.58
Std. Dev.	1.2	1.3	
Median	1.0	1.1	
Min - Max	0 - 6.2	0 - 6.6	
Q1 - Q3	0.3 - 1.6	0.5 - 1.7	
9 Months	(n=46)	(n=63)	
Mean	1.5	1.3	0.38
Std. Dev.	1.1	1.1	
Median	1.3	1.1	
Min - Max	0 - 4.8	0.10 – 6.0	
Q1 - Q3	0.90 - 2.1	0.65 - 1.8	
15 Months	(n=49)	(n=57)	
Mean	1.6	1.4	0.57
Std. Dev.	1.5	1.2	
Median	1.23	1.1	
Min - Max	0 - 6.6	0 - 5.4	
Q1 - Q3	0.8 - 2.0	0.5 - 2.0	

Q1 = first quartile; Q3 = third quartile

[§]P-value from Wilcoxon rank sum test using the t approximation

Table 6

Stimulated Whole Salivary Production of Study Groups

	Pilocarpine	ALTENS	P-value[§]
Baseline	(n=65)	(n=68)	
Mean	2.3	2.4	0.82
Std. Dev.	1.7	1.8	
Median	1.9	2.0	
Min - Max	0.20 - 10	003- 9.6	
Q1 - Q3	1.0 – 3.0	0.97 - 3.2	
4 Month	(n=47)	(n=57)	
Mean	2.6	2.7	0.86
Std. Dev.	1.8	1.9	
Median	2.2	2.4	
Min - Max	0 - 8.1	0 - 10	
Q1 - Q3	1.4 - 3.3	1.4 - 3.6	
6 Month	(n=44)	(n=54)	
Mean	2.5	2.9	0.66
Std. Dev.	1.7	2.4	
Median	2.2	2.1	
Min - Max	0.20 – 8.0	0 - 13	
Q1 - Q3	1.0 - 3.4	1.5 - 3.8	
9 Month	(n=44)	(n=58)	
Mean	3.2	3.0	0.61
Std. Dev.	1.9	2.0	
Median	3.0	2.8	
Min - Max	0.1 – 8.0	0.11 – 9.0	
Q1 - Q3	1.8 - 4.9	1.6 - 3.9	
15 Month	(n=47)	(n=54)	0.95
Mean	2.8	2.9	
Std. Dev.	2.1	2.5	
Median	2.6	2.2	
Min - Max	0 - 7.8	0 - 9	
Q1 - Q3	1 - 4.4	1.1 - 4.4	

Q1 = first quartile; Q3 = third quartile.

[§]P-value from Wilcoxon rank sum test using normal approximation