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# Salivary electrostimulation in the treatment of radiotherapy-induced xerostomia (LEONIDAS-2): a multicentre, randomised, double-masked sham-controlled phase 3 trial

**Short running title: The LEONIDAS-2 study**

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**Abstract**

**Purpose**: Radiotherapy-induced xerostomia (RIX) significantly affects quality of life in head and neck cancer (HNC) survivors. Neuro-electrostimulation of the salivary glands may safely increase natural salivation and reduce dry mouth symptoms.

**Methods and Materials**: Multicentre double-masked randomised sham-controlled clinical trial to assess the long-term effects of a commercially available intra-oral neuro-electrostimulating device in lessening xerostomia symptoms, increasing salivary flow and improving quality of life in individuals with RIX. Using a computer-generated randomization list, participants were assigned (1:1) to an active intra-oral custom-made removable electrostimulating device or a sham device to be used for 12 months. The primary outcome was the proportion of patients reporting a 30%

improvement on the xerostomia VAS at 12 months. A number of secondary and exploratory outcomes were also assessed through validated measurements (sialometry and VAS) and quality of life questionnaires (EORTC QLQ-H&N35, OH-QoL16 and SF-36).

**Results**: As per protocol, 86 participants were recruited. Intention-to-treat analyses showed no statistical evidence of a difference between the study groups with respect to the primary outcome or for any of the secondary clinical or quality of life outcomes. Exploratory analyses showed a statistically significant difference in the changes over time of the dry mouth sub-scale score of the EORTC QLQ-H&N35 in favour of the active intervention.

**Conclusion**: LEONIDAS-2 did not meet the primary and secondary outcomes.

**Funding:** NIHR Research for Patient Benefit Programme

**Introduction**

Head and neck cancer (HNC) is the seventh most common cancer worldwide (1) and is often managed with radiotherapy, either alone or in association with chemotherapy and/or surgery (2). Persistent dry mouth is the most common late adverse effect of radiotherapy to the head and neck (3), with irreversible salivary gland damage (hypofunction) developing in 63-93% of the HNC survivors (4). The insufficient wetting and oral mucosa lubrication associated with reduced salivation can cause notable difficulties with speaking, swallowing, taste and mastication (5), as well as an increase in the risk of oral disease (e.g. dental caries) (6). Overall it can lead to a substantial reduction in the quality of life of affected individuals (7).

Management of dry mouth of radiotherapy is notoriously challenging. The interventions offered to patients vary widely among HNC centres (8), and guidance for clinicians, where available, is often not evidence-based (9). The UK National Multidisciplinary Guidelines for Head and Neck Cancer recommend that xerostomia should be managed with sipping fluids, the use of topical sialagogues (gum or lozenges), salivary substitutes (as a gel or mouthwash), or the cholinergic agonist pilocarpine (10). However, our previous meta-analysis shows that only the use of cholinergic agents pilocarpine and cevimeline is supported by robust evidence, whereas there remains no evidence, or very weak evidence, that other interventions can reduce dry mouth symptoms or increase salivary flow in this population (11). As frequent adverse effects limit the widespread use of cholinergic agents, there remains the need to investigate other interventions with a safer profile.

Saliva secretion is controlled by dual innervation from the autonomic nervous system through a reflex arc comprised of afferent nerves, central salivary nuclei, and efferent nerves (12). The application of electrical stimuli to one of the components of the salivary reflex may increase salivary secretion and potentially lessen xerostomia symptoms (13). Animal studies have shown that electrostimulation can, indeed,

enhance salivary production (14,15). A number of intra-oral salivary electrostimulating devices intended for human use have been introduced over the years (16,17), with relevant clinical studies suggesting possible clinical benefits in individuals with xerostomia due to a number of causes (13,18-21). However, the evidence supporting efficacy in HNC survivors is scarce, as available studies included very few participants with radiotherapy-induced xerostomia. The aim of the present study was to evaluate the efficacy of salivary electrostimulation in reducing distressing dry mouth resulting from radiotherapy in HNC survivors. We tested the hypothesis that the long-term application of a novel removable intraoral neuro-electrostimulating device would reduce dry mouth symptoms, increase salivary function and improve quality of life.

**Methods and materials**

LEONIDAS-2 (*long-term evaluation of the effectiveness of a novel intra-oral electrostimulator for the treatment of radiotherapy-induced xerostomia*) was a parallel group, double-masked, multicentre sham-controlled randomised trial, which randomised participants 1:1 to 12 months of therapy with a removable active intra-oral neuro-electrostimulating device or a sham device (providing tactile but not electrical stimulation). The study was undertaken in two clinical centres in UK (University College London Hospital and Bradford Royal Infirmary) by clinicians with expertise in the management of HNC and late adverse effects of radiotherapy to the head and neck (Oral Medicine specialists, Head and Neck Surgeons, and Clinical Oncologists). Two additional sites contributed as patient identification centres (PICs) and referred patients to University College London Hospital for eligibility assessment. The full list of study inclusion and exclusion criteria is presented in Data Supplement 1. In brief, patients were deemed eligible if they had a history of 40Gy or more of radiotherapy to the head and neck, notable persistent dry mouth symptoms in keeping with grade 1 or 2 of RTOG/EORTC Late Radiation Morbidity Scoring

Schema for salivary glands (22), and a minimum subjective degree of dryness of 50mm (≥50mm) on a 0-100mm Visual Analogue Scale [VAS] scale (0=no dryness; 100 =maximum dryness) (23), as well as evidence of residual salivary gland function demonstrated through any increase in salivary flow on stimulation via chewing paraffin wax.

LEONIDAS-2 received favourable opinion by the Leeds West Research Ethics Committee (11/YH/0072) and was sponsored by the University College London (Project ID: 11/0138). The trial was undertaken in accordance with Declaration of Helsinki (24) and the International Conference on Harmonisation Good Clinical Practice guidelines (25). The study is reported accordingly to the CONSORT guidelines (26).

**Study device**

The device tested in LEONIDAS-2 was a CE-marked second-generation removable custom-made intra-oral salivary neuro-electrostimulator manufactured by Saliwell Ltd (Israel). It consists of a consisting of a C-shaped mouthguard-like mouthpiece made to fit the lower dental arch and provided with an associated infrared remote control to activate or deactivate the electrical stimulation. The devices were individually manufactured for each participant using a mould of the lower dentition (or lower mandibular ridge in edentulous patients). Polyvinylsiloxane impressions (Aquasil Ultra Medium-Heavy Body, Dentsply) were taken by dentally-trained Maxillofacial Surgeons and/or Oral Medicine specialists as per established technique and posted to the manufacturer. All devices contained an electronic circuit with a microprocessor, a receiver of remote control signals, a power source of two 3V small coin batteries all embedded and hermetically sealed between two sheets of dental grade acrylic plastic. The devices had two stimulating electrodes protruding from one side of the plastic sheets so to contact the oral mucosa of the posterior inner aspect of the mandible, nearby the third molar (Figure 1). On delivery and fitting of the customised devices onto participants' lower jaw, fine adjustments were made where

necessary to ensure direct contact between the electrodes and the oral mucosa, as well as comfort during use. Adjustments consisted of removing a thin layer of acrylic plastic and/or trimming the electrodes with a dental burr handpiece, and were performed at the discretion of the attending study investigators.

The electrical stimulation was achieved in the active devices by the delivery of low-power, low-voltage, biphasic pulses from the electrodes through the oral mucosa to the nerve pathways of the salivary gland reflex (afferent, efferent or both). The devices were switched on and off by pressing the relevant buttons of the remote control, respectively, with a green light on the electronic circuit blinking to show that the device had received the signal from the remote. Only the active devices released electric stimuli when switched on. In case of device failure (device's light not responding to remote control), a first attempt was made to change the batteries of the remote control. In the event of a permanent failure, a new individual customized device was manufactured.

**Randomisation**

Patients were randomly assigned in a 1:1 ratio to the use of the active neuro-electrostimulating device or a sham device. Blocked randomisation lists (block size 4) stratified by centre were prepared by an independent statistician (DM). The method of sequence generation was a random-number generator on a computer. Study investigators and participants were masked to the intervention and the active and sham devices, as well as the associated remote controls, were identical in appearance, pre-packed in identical boxes and consecutively numbered for each participant according to the randomisation schedule. The randomisation code remained concealed until all patients completed the study visits and the database was finalized.

**Procedures**

Potentially eligible participants were identified in the HNC and/or Oral Medicine outpatient clinics of the study sites, provided with verbal and written information

about the study, and invited to attend the screening visit for eligibility confirmation after obtaining written consent. As the study was designed to include individuals with residual salivary gland function, unstimulated (resting) whole saliva and paraffin chewing-stimulated whole saliva were collected during the screening visit. All subjects were instructed to refrain from smoking, eating, drinking or tooth brushing at least 90 minutes prior to saliva collection. Unstimulated whole saliva was collected for 5 minutes using an established spitting technique (27). During the stimulated whole saliva collection, the subjects chewed a piece of tasteless parafilm (5×5cm, 0.30g; Parafilm, Fisher Scientific, UK) at their natural pace. Saliva volumes were determined gravimetrically (assuming 1g = 1mL), using pre-weighted tubes (Sterilin, UK, catalogue n.185CM) and a precision balance (Scout Pro SPU123, Ohaus, NJ), with saliva flow rates expressed in millilitres per minute (mL/min). The grade of xerostomia at screening was assessed using the dedicated RTOG/EORTC Late Radiation Morbidity Scoring Schema and the xerostomia VAS score (0-100mm). Individuals meeting all the inclusion criteria and none of the exclusion criteria were invited to enter the study (Data Supplement 1). An impression of the lower dentition (or the lower ridge in edentulous patients) was taken from all study participants at the end of the screening visit and sent to the manufacturer. The devices were manufactured, sent directly to the study sites, and delivered to study participants during the second study visit (baseline). The participants were asked to use the device not longer than 5 minutes per hour, as many times as they wanted during the day. Written manufacturers' instructions were also provided. At the baseline study visit, the salivary flow rate was measured and study questionnaires were completed and collected. Similar measurements were performed during the subsequent study visits at the end of month 1, 2, 4, 6, 8 and 12, with the visits running preferentially at the same time of the day as the baseline study visit so to minimise fluctuations related to the circadian rhythm of salivary secretion. Participants were also asked to complete a diary of the frequency of application of the device per day.

**Outcomes**

The outcome measure for the primary objective of xerostomia relief was a 30% reduction in dry mouth symptoms based on 100-mm long VAS (100mm=maximum dryness) at 12 months compared with pre-treatment (baseline). The minimal clinically important difference for dry mouth VAS score in the HNC population is unknown, therefore the cut-off of 30% reduction from baseline was chosen to promote homogeneity with previous studies that used the same xerostomia outcome measure (28,29).

The outcome measure used for the secondary objective of assessing changes in salivary gland function was a 5-minute collection of unstimulated whole salivary flow as detailed above. We also used the 100mm VAS for xerostomia as a continuous outcome for the secondary objective of examining changes in VAS scores without a pre-defined cut-off. With respect to the secondary objective of assessing the changes in the quality of life, the following three instruments were used: the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire head and neck cancer-specific supplementary module (QLQ-H&N35) (30), the Oral health-related quality-of-life measure (OH-QoL16) (31) and the Short Form-36 (SF-36) questionnaire (32). With respect to the EORTC QLQ-H&N35 the multi-item scores of swallowing, senses, speech and social eating and the single-item score of dry mouth, sticky saliva, and coughing were considered to be clinically relevant and selected for data analysis. For the OH-QoL16, the overall score was considered for data analysis. With respect to the SF-36 the following five domains were considered clinically meaningful to the study intervention and objectives, and relevant to data analysis: general health perception, physical role functioning, social functioning, mental health, and reported health transition. For all questionnaires scores were calculated as per relevant manuals (31-33). Additional details regarding the included patient-reported outcome measures are provided in Data Supplement 2.

**Sample size**

Sample size was calculated with regard to the primary outcome (≥ 30% reduction in xerostomia symptoms at 12 months from baseline): assuming that 20% of the participants in the control group and 60% of those using the active device would meet the primary outcome, the sample size required to detect such a difference in reduction of xerostomia symptoms with 90% power using a significance level of 5%, was 70. A potential drop-out rate of 20% was estimated on the basis of (i) expected recurrence rate of HNC post-treatment and (ii) study duration, bringing the total number of participants needed to 84.

**Statistical analysis**

Statistical analyses were performed following a predefined statistical analysis plan using STATA software (version 14). All analyses were carried out on an intention-to-treat basis including all the participants who received their allocated intervention according to their original randomised group assignment. Those with missing data were excluded from analyses and assumed to be missing at random.

For the purpose of the primary analysis, proportions were compared using a Fisher's exact test reported alongside an odds ratio and difference in proportions with associated 95% confidence intervals. In further analyses, multiple logistic regression models were fitted to obtain odds ratios adjusted initially for age, centre and gender and a further model including predefined prognostic factors (IMRT vs. conventional radiotherapy, number of residual salivary glands and years since radiotherapy completion).

For the secondary outcomes of dry mouth VAS scores (continuous score without a predefined cut-off), sialometry, and quality of life questionnaire scores at 12 months, data were compared between randomised groups using appropriate regression models with adjustment for baseline scores and centre. In most cases, ordinary least squares regression was appropriate, however for the EORTC single item scales, which provide ordinal outcomes, proportional odds models were used. Additional

models adjusting for the same factors specified for the primary analysis were also fitted.

In exploratory analyses, we used repeated measurements of outcomes collected at the end of month 1, 2, 4, 6, 8 and 12 in order to gain a better understanding of the effect of the intervention over time and to assess whether salivary electrostimulation might be associated with a cumulative effect (increased divergence between treatments over time) or the development of tolerance (reduced divergence between treatments over time). Outcomes considered included dry mouth VAS scores, sialometry, and quality of life questionnaire scores. We looked at trends in the repeated measurements using graphs for non-categorical outcomes and then fitted mixed effects models to estimate the average treatment effect over the 12-month duration and to investigate treatment by time interactions.

For all outcomes the characteristics of patients with missing values were examined and compared with those without missing values. Sensitivity analyses were carried out adjusting treatment effects for baseline factors related to missingness. Information about the frequency of use of the device, withdrawals and adverse events was summarised descriptively.

**Role of funding source**

Funding was provided by a NIHR Research for Patient Benefit grant (PB-PG-0909-20063), and further staff support was received from the NIHR Clinical Research Network North Thames and the NIHR UCLH Biomedical Research Centre. The manufacturer Saliwell Ltd provided the study devices at reduced price for research purpose, and had no role in study design, collection, analysis, interpretation of data, or writing of the report.

**Results**

***Study groups and demographics***

Between January 2012 and November 2013, a total of 141 patients were assessed for eligibility and 86 participants were included and randomised to the use of the

active neuro-electrostimulating device (n=43) or a sham device (n=43) (Figure 2). Randomisation groups were well matched at baseline with regard to demographics, radiotherapy regimen and dosage of radiotherapy to primary tumour (Table 1). The median unstimulated salivary flow was 0.07 mL/min (IQR 0.04 to 0.15) for the group receiving the sham device and 0.09 mL/min (IQR 0.04 to 0.14) for those receiving the active device. Approximately half of the participants (56% in the sham group vs. 58% in the active group) had received IMRT. The mean dose to the primary tumour was 64Gy (mean dose in the sham group was 64.4, SD 2.81 vs 64, SD 3.27 in the active group).

***Device use***

The average number of device applications per day in the active and sham group over 12 months was 2.5 (SD 1.48) and 2.1 (SD 1.53), respectively, with an average daily cumulative use of 12.5 and 10.5 minutes, respectively.

***Device replacement***

Device replacement was required for 10 participants because of malfunction. While waiting for the replacement, which took an average of 8 weeks, participants were asked to use the malfunctioning device as normal.

***Dropout rate***

Thirty-six of the 43 individuals randomized to the sham group and thirty-two of the 43 individuals randomized to the active group completed the study (Figure 2). Two participants in the active group did not receive the allocated intervention as their radiotherapy-induced fibrosis (trismus) worsened quickly after randomization, therefore preventing the completion of the clinical procedures needed to manufacture the customised device. Overall attrition rate was 20.9%, as anticipated in the sample size calculation. The dropout rate was higher in the active group compared to the sham group (25 % vs. 16%), although this difference is influenced by the two participants who did not receive the intervention due to fibrosis development.

***Primary Outcome***

The primary outcome was achieved by 31% of participants in the sham group and 22% in the active group (Table 2). In the unadjusted analyses, there was no significant difference between the active and sham groups (difference in proportions: -0.09 [95% confidence interval (CI) -0.30, 0.12]; odds ratio (OR) 0.64 [95% CI 0.18, 2.16], P=0.58). The adjusted models showed similar results (OR adjusted for centre, age and gender: 0.50 (95% CI 0.15, 1.74) P=0.28; OR adjusted for age, gender, type of radiotherapy, years since radiotherapy completion, and number of residual salivary glands 0.43 [95% CI 0.11, 1.64], P= 0.22).

***Secondary Outcomes***

*VAS dry mouth score and unstimulated salivary flow rates at 12 months*

There was no significant difference between the randomised groups for the mean VAS scores after 12 months of treatment (Data Supplement 3) in both the model adjusted for baseline VAS and centre and the models adjusted for other factors (fully adjusted model -0.05 [95% CI -1.13, 1.03], P= 0.93). Similarly, there was no evidence of a difference in the mean unstimulated salivary flow rates at 12 months in all analyses (Table 3) (fully adjusted model -0.012 [95% CI -0.10, 0.08], P= 0.78). Because of concerns about non-normality of sialometry measurements, analyses for this outcome were also carried out after a square root transformation. These analyses gave similar conclusions to those reported (based on untransformed data).

*EORTC QLQ-H&N35, OH-QoL16 and SF-36 scores at 12 months*

For all the pre-specified EORTC QLQ-H&N35 multi-item and single item sub-scores, summary statistics were similar between the randomised groups and there were no statistically significant differences identified (Data Supplement 4-5) in unadjusted or adjusted models. For the OH-QoL16 overall scores at 12 months, analyses adjusted for baseline and centre showed some evidence of a slightly lower average score for the active group compared with the sham group (Difference in means: -3.68 [95% CI -7.58 to 0.21; P=0.06]). On further adjustment however, the results were not significant (P=0.11) (Data Supplement 6). Differences between groups for the pre-

planned SF36 domain scores were small and not statistically significant in either the unadjusted or adjusted analyses (Data Supplement 7).

***Exploratory Outcomes***

*Changes in VAS score and unstimulated salivary flow rates over time (analysis of repeated measurements)*

Graphical assessment of the mean VAS scores over time [measured at the end of months 1, 2, 4, 6, 8 and 12] (Data Supplement 8) showed that VAS score reduced similarly in both groups over time with a suggestion of greater improvement for the active group over the first 6 months. There was no statistically significant difference between the groups over the total study period (model adjusted for baseline value, visit and centre: difference in means (active-sham) -0.55 [95% CI -1.26, 0.17], P= 0.14; fully adjusted model -0.49 [95% CI -1.27, 0.28], P= 0.21) (Data Supplement 9) and no evidence that the effect changed over time (interaction P-value=0.20). Graphical assessment of the mean sialometry scores over time (Data Supplement 10) showed that salivary flow rates increased over time similarly in both groups. There was no statistically significant difference between the groups (model adjusted for baseline value, visit and centre -0.0004 [95% CI -0.059, 0.058], P= 0.99; fully adjusted model -0.012 [95% CI -0.072, 0.048], P= 0.69) and no evidence that the trend over time differed by randomised group (interaction P-value=0.67) (Data Supplement 11). There was, therefore, no evidence of a cumulative effect or tolerance development to the effect of the device over time with respect to VAS and sialometry scores.

*Changes in EORTC QLQ-H&N35, OH-QoL16 and SF36 scores over time (analysis of repeated measurements).*

Graphical assessment of the EORTC QLQ-H&N35 multi-item domain mean scores over time showed that scores tended to decrease in both groups with a suggestion of greater improvement in quality of life for the active group over the first 6 months (Data Supplement 12). Mixed effects models, however, showed no evidence of

statistical differences between the randomised groups across the repeated measurements and no evidence of treatment by time interaction (Data Supplement 13).

With regards to the repeated measurements of the pre-planned EORTC QLQ-H&N35 single item sub-scale scores included in our analyses (Table 4), there was evidence of a statistically significant difference between groups over 12 months with respect to the dry mouth item score indicating a beneficial effect of the active intervention compared to sham device (fully adjusted model OR 0.37 [95% CI 0.14, 0.97], P= 0.04), which did not change significantly over time (Interaction P-value=0.26). Clinically this indicates that the odds of having a better score for dry mouth on the active treatment are 67% higher than for the control over the 12 months since baseline (after adjusting for predefined prognostic baseline factors). The difference was not statistically significant for sticky saliva (fully adjusted OR 1.35 [95% CI 0.57, 3.22], P= 0.49, Interaction P-value = 0.85) and cough score (fully adjusted OR 0.68 [95% CI 0.35, 1.87], P= 0.45, Interaction P-value = 0.15).

Graphical assessment of the mean OH-QoL16 overall score over time showed that scores increased over time similarly in both groups with regards to physical role functioning with mental health (Data Supplement 14). There was no statistically significant difference between the groups in all models (Data Supplement 15) and no evidence of a treatment group interaction with time.

Graphical assessment of the pre-planned SF36 domain mean scores over time (Data Supplement 16) suggested a trend for a greater increase in score (better functioning) for role physical and mental health in the active group compared to the sham group, with the opposite noted for general health and social functioning. There was no statistically significant difference on mixed effect models between the groups for any of the domain scores over 12 months, with the exception of health transition domain which showed higher (worse) scores for the active group at later time points (Data Supplement 17).

***Sensitivity Analyses***

Sensitivity analyses, which were carried out to adjust for any baseline factor that was related to missingness, did not impact on the overall conclusions.

***Adverse events***

The intervention was well tolerated among participants. There were two unrelated serious AEs (SAEs) per arm (Data Supplement 18). A total of forty-seven adverse events (AEs) were reported, of which four (8%) were likely related to the study intervention including transient pain to the site where the device electrodes contact the mucosa, frictional damage to the oral mucosa leading to bone exposure and superficial osteonecrosis, and recurrent parotid gland swelling upon device application; furthermore, a participant randomized to the sham device required a chest and abdominal X-ray (which showed no abnormality) to investigate whether he had inhaled or ingested a missing small component (one of the two electrodes) of the device.

In two out of 4 cases (parotid gland swelling and osteonecrosis) the AE resulted in the participants' decision to withdraw from the study intervention and successive study visits.

**Discussion**

RIX is a major cause of reduced quality of life in H&N cancer survivors (7). There remains little robust evidence to guide clinicians in the management of distressing dry mouth symptoms in HNC survivors, mostly due to the lack of well-designed randomised controlled trials in the post-radiotherapy setting, only exception being the cholinergic agents pilocarpine and cevimeline (11). Salivary gland neuro-electrostimulation in the treatment of dry mouth disorders was first introduced more than 30 years ago (19), however LEONIDAS-2 is the first double-masked randomized controlled trial of long-term salivary neuro-electrostimulation in head and neck cancer survivors.

LEONIDAS-2 results show that the active device did not perform significantly better

than the sham device, leading to the primary outcome of the study (30% reduction in VAS dry mouth score at 12 months) not being met. Similarly, with respect to the secondary outcomes of the changes in salivary flow rates, continuous VAS score, and quality of life scores (OH-QoL16, SF-36 and EORTC QLQ-H&N35) at 12 months, we observed no significant difference between the two study groups. In exploratory analyses, we used repeated measurements of outcomes collected at the end of month 1, 2, 4, 6, 8 and 12 to gain a better understanding of the effects of the intervention over time. We also wished to assess whether the use of the active device could be associated with a cumulative effect or the development of tolerance over time. Exploratory analyses result relevant to the VAS, salivary flow, and the OH-QoL16 score changes over time showed no notable differences between the two groups and no evidence of cumulative effect or tolerance development. Similarly, the changes over time in the multi-item domains scores of EORTC QLQ-H&N35 were not different between groups. However, the single item dry mouth score of EORTC QLQ-H&N35 showed a statistically significant difference in favour of the active intervention, which was consistent across the predefined time-points. We also observed that the changes over time in the pre-planned SF36 domain scores between the groups were not different, with the exception of the health transition domain score changes, which showed a statistically significant difference in favour of the sham intervention at later time points.

In summary, LEONIDAS-2 did not show evidence of a benefit of the device on the primary and secondary trial outcomes. Nonetheless, exploratory analysis of changes over time, which is particularly relevant for longitudinal studies of interventions for chronic diseases (34), indicates a reduction in one of the self-reported measures of the dry mouth symptoms. This finding, although suggesting with low confidence some possible beneficial effects of salivary electrostimulation upon patient symptoms, should be interpreted with caution, as patient-related outcome measures are prone to adaptation bias (35).

There are a number of factors related to LEONIDAS-2 design and execution that may have negatively affected the study outcomes. One or more adjustments in the shape and size of the manufactured devices were required to ensure comfortable fitting and adequate contact between the electrodes and the oral mucosa, and were pragmatically performed by the study investigators during trial visits. These adjustments were heavily operator-dependent, and may have introduced variability in the delivery of electric stimuli as well as in the comfort of the device, with consequent impact upon willingness of participants to use the intervention frequently. Of note, the manufacturer has since developed a new one-size-fits-all electrostimulating device that does not require operator-dependent adjustments and ensures a comfortable contact with the oral mucosa (https://www.saliwell.com).

The selection of the primary outcome is also worth discussing, as trials results may be negatively affected by an outcome that is not meaningful or well suited to the trial purpose (36). The primary outcome of LEONIDAS-2 (≥ 30% reduction from baseline in xerostomia symptoms at 12 months on a 100mm VAS) was chosen to promote homogeneity across clinical trials of dry mouth interventions (28,29). Nevertheless, there remains no robust evidence that such an ambitious outcome may indeed be meaningful to the HNC patient group, or that a 30% difference may adequately capture a change in dry mouth symptoms that patients would find beneficial. Other studies have used a cut-off of 25 or 20mm on a 0-100mm VAS, or linear changes in VAS score without a cut-off (11). Considering the lack of consensus core outcomes for radiotherapy-induced dry mouth and in the absence of robust studies defining the minimally clinical important change in VAS or other scales for this population, it is possible that LEONIDAS-2 results may have been negatively affected by a predefined arbitrary outcome with an unrealistic magnitude change.

Furthermore, the HNC patient focus group contributing to LEONIDAS-2 design suggested a maximum length of use of the device of 5 minutes per application, whereas previous pilot trials of the same device had allowed participants using the

device for up to 10minutes (13,21) per application. Overall, the average duration of electrostimulation per day in LEONIDAS-2 was 10-12 minutes (an average of two applications per day), whereas in previous trials participants had used the same device for an average of 20-40 minutes per day (13,21). It is therefore possible that LEONIDAS-2 results may have been, at least in part, negatively affected by an inadequately short time of application of the study intervention. Another important limitation of our study includes the small sample size and the consequent inability to stratify the results based on parotid mean radiotherapy dose, which is known to be closely correlated to the development of permanent salivary gland dysfunction and xerostomia (37). We note that the mean dose to the primary tumour was 64Gy, which is considerably higher than the maximum dose recommended to aid salivary function recovery (24–26 Gy). Also, considering that some spontaneous recovery in salivary gland function can be observed up to 3 years post-radiotherapy (38-40), it is possible that a higher number of participants in the sham group (median time from radiotherapy: 3.5 years) may have experienced some spontaneous improvement in salivary gland function as compared to the active intervention group (median time from radiotherapy: 5 years), thus potentially masking or diluting the differential effects of the active vs sham device. We have however performed adjusted statistical analyses taking this into account. Furthermore, participants recruited at late time point after radiotherapy may present with established parenchymal damage that may be difficult to reverse.

It is also relevant to note that the participants in the present study had been treated with the radiotherapy techniques available a few years prior to recruitment (more than 10 years ago). Therefore, they may not fully represent the current cohort of HNC survivors, where all patients have received IMRT leading to a significantly lower dose to the salivary tissue and, hypothetically, a possible better response to salivary electrostimulation.

Finally, as it is assumed that mechanical/tactile stimulation can trigger a temporary

increase in salivation, it is possible that in some patients the capacity of the irradiated salivary gland tissue to increase secretion may be limited and easily exhausted by mechanical/tactile stimulation, therefore preventing the additional electric stimulation of the active device to result into a larger increase in salivation.

**Conclusions**

LEONIDAS-2 did not meet the primary outcome of xerostomia relief. The secondary outcomes of increased salivation and improved quality of life were not met either. Although exploratory analyses showed a statistically significant reduction in one of the dry mouth indicators, there remains a low degree of confidence and no robust convincing evidence that meaningful benefits may be reasonably expected from the salivary electrostimulating device used in the study. Further research on the effects of salivary electrostimulation in HNC survivors is warranted in order to overcome the limitations of the present study. We suggest that future trials should (i) use the new generation one-size-fits-all, easy-fitting and not operator-dependant electrostimulating device, (ii) complete preparatory work relevant to the identification of the most appropriate and clinically meaningful endpoints and outcome measures, and (iii) ensure homogeneity or participant stratification on the basis of the parotid mean dose and time from completion of radiotherapy.



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**Conflict of interest**

No conflict of interest

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**Data sharing statement**

Data sharing statement: The authors agree to share anonymized data upon reasonable request by researchers.

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**Figure captions**


Figure 1 Second generation electrostimulating device (Saliwell GeNarino)

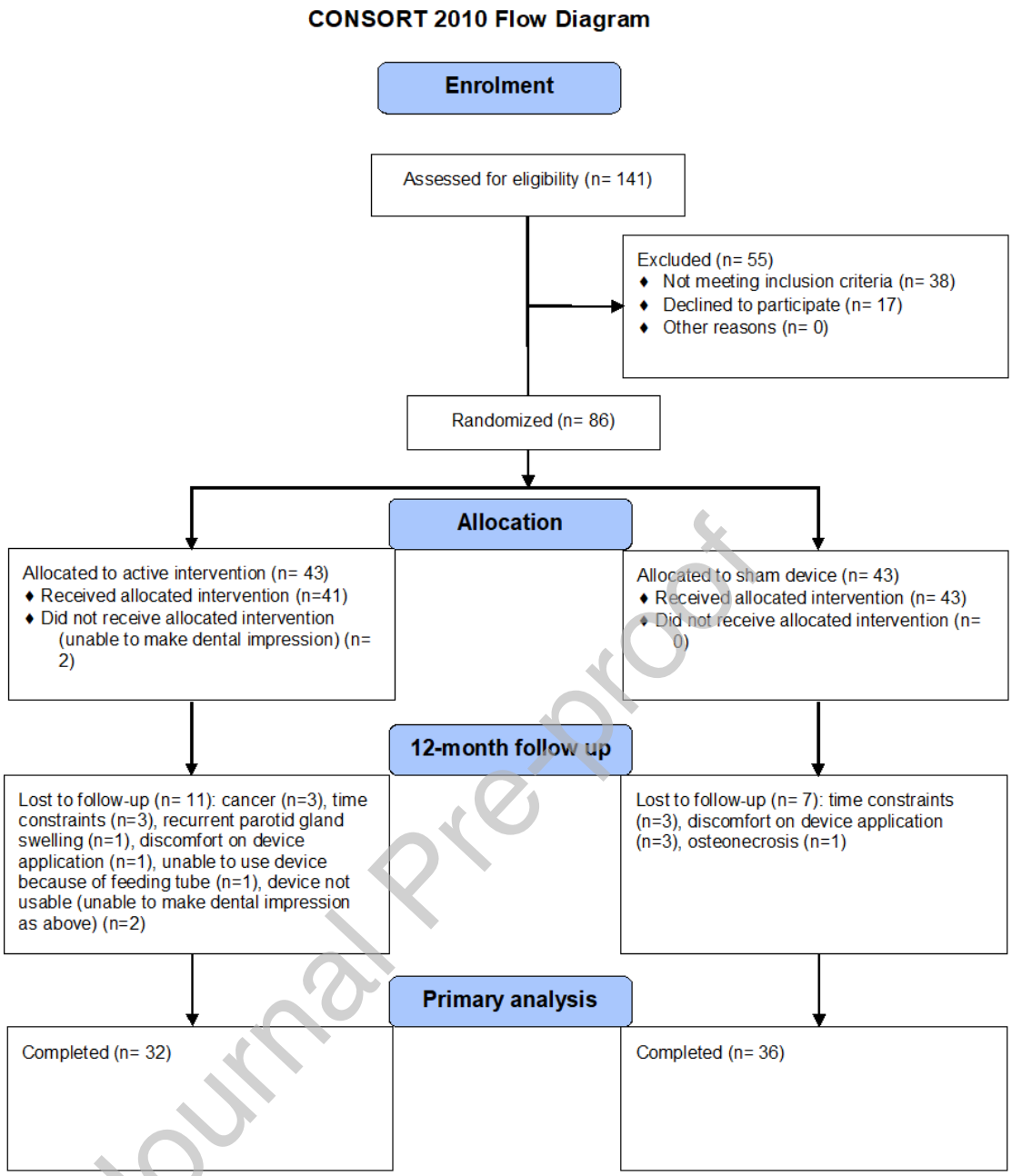


Figure 2 Trial Profile

## Tables

Table 1 Baseline characteristics of patients (numbers are frequency (%) unless otherwise stated. SD= standard deviation, IQR = interquartile range)

| | | Sham pacemaker (n=43) | Active pacemaker (n=43) |
|---|---|---|---|
| Age at baseline (years) | Mean (SD) | 58.2 (9.3) | 58.4 (10.8) |
| Gender | Male | 31 (72%) | 35 (81%) |
| | Female | 12 (28%) | 8 (19%) |
| Smoker | Yes | 4 (9%) | 5 (12%) |
| | No | 39 (91%) | 38 (88%) |
| Ethnic group | Caucasian | 40 (93%) | 38 (88%) |
| | Other | 3 (7%) | 5 (12%) |
| Alcohol (units/week) (0 for non-drinkers) | Median (IQ range) | 1 (0 to 5) | 2 (0 to 5) |
| Alcohol drinker | Yes | 23 (53%) | 24 (56%) |
| | No | 20 (47%) | 19 (44%) |
| Site of first cancer (n=84) | Oral cancer | 7 (17%) | 4 (10%) |
| | Oropharyngeal | 22 (53%) | 24 (57%) |
| | Pharynx | 3 (7%) | 1 (2%) |
| | Hypopharynx | 2 (5%) | 1 (2%) |
| | Larynx | 1 (2%) | 0 |
| | Salivary gland | 1 (2%) | 2 (5%) |
| | Other | 6 (14%) | 10 (24%) |
| Stage of Primary Tumour (n=74) | I | 4 (11%) | 4 (11%) |
| | II | 2 (5%) | 3 (8%) |
| | III | 10 (28%) | 5 (13%) |
| | IV | 20 (56%) | 26 (68%) |
| Type of Radiotherapy | Conventional | 19 (44%) | 18 (42%) |
| | IMRT | 24 (56%) | 25 (58%) |
| Dosage of radiotherapy to primary tumour [Gross Tumour Volume - GTV] (Gray) | Mean (SD) | 64.37 (2.81) | 64.00 (3.27) |
| Years since Radiotherapy completion | Mean (SD)<br>Median (IQ range) | 4.71 (2.93)<br>3.5 (3 to 6) n=38 | 5.14 (2.92)<br>5 (3 to 6) n=43 |
| Xerostomic medical condition | Yes | 10 (23%) | 6 (14%) |
| | No | 33 (77%) | 37 (86%) |
| Xerostomic medication | Yes | 14 (33%) | 13 (30%) |
| | No | 29 (67%) | 30 (70%) |
| Chemotherapy | Yes | 37 (86%) | 31 (72%) |
| | No | 6 (14%) | 12 (28%) |
| Surgery to primary site | Yes | 25 (58%) | 24 (56%) |
| | No | 18 (42%) | 19 (44%) |
| Salivary flow rate (ml/min) (at screening) | Median (IQ range)<br>Mean (SD) | 0.07 (0.04 to 0.15)<br>0.12 (0.12) | 0.09 (0.04 to 0.14)<br>0.13 (0.15) |
| Dry mouth symptoms VAS (at screening) | Mean (SD) | 7.44 (1.59) | 6.99 (1.47) |
| EORTC QLQ-H&N35 | | | |
| Swallowing | Mean (SD) | 29.34 (23.94) n=41 | 29.56 (21.08) n=42 |
| Senses | Mean (SD) | 37.40 (27.08) n=41 | 37.30 (29.40) n=42 |
| Speech | Mean (SD) | 24.93 (23.14) n=41 | 23.02 (18.43) n=42 |
| Social eating | Mean (SD) | 38.62 (28.67) n=41 | 39.48 (26.93) n=42 |
| Dry mouth (n=85) | Not at all/ a little | 4 (10%) | 3 (7%) |
| | Quite a bit/ very much | 37 (90%) | 39 (93%) |
| Sticky saliva (n=82) | Not at all/ a little | 18 (44%) | 20 (49%) |
| | Quite a bit/ very much | 23 (56%) | 21 (51%) |
| Coughing | Not at all/ a little | 33 (80%) | 30 (71%) |
| | Quite a bit/ very much | 8 (20%) n=41 | 12 (29%) |
| OH-QoL16 overall score | Mean (SD) | 44.09 (7.45) n=39 | 45.43 (10.35) n=42 |
| SF36 | | | |
| General health perception | Mean (SD) | 56.55 (21.93) n=40 | 56.87 (19.73) n=42 |
| Physical role functioning | Mean (SD) | 46.79 (41.82) n=39 | 57.74 (40.76) n=42 |
| Social role functioning | Mean (SD) | 73.13 (23.78) n=40 | 74.11 (26.39) n=42 |
| Mental health | Mean (SD) | 72.53 (15.75) n=40 | 70.57 (20.22) n=42 |
| Reported health transition (n=82) | Better than a year ago | 25 (63%) | 27 (64%) |

Table 2 Results from analysis of primary outcome

| ≥ 30% reduction in dry mouth symptoms (from screening)? (n=67) | Sham (n=36) | Active (n=32) | |
|---|---|---|---|
| Yes | 11 (31%) | 7 (22%) | |
| No | 25 (69%) | 25 (78%) | |
| | | | |
| | Estimate (Active vs Sham) | 95% Confidence interval | P-value |
| Difference in proportions | -0.087 | (-0.295 to 0.121) | |
| Odds ratio | 0.64 | (0.18 to 2.16) | 0.58 (exact) |
| Odds ratio adjusted for centre, age, gender (n=68) | 0.50 | (0.15 to 1.74) | 0.28 |
| Odds ratio adjusted for centre, age, gender, Type of radiotherapy, years since radiotherapy completion, Number of residual salivary glands (n=64) | 0.43 | (0.11 to 1.64) | 0.22 |

Table 3 Results from analysis of continuous 12-month salivary flow rate (ml/min)

| Salivary flow rate (ml/min) | Mean (SD) / Median (IQR) | | Difference in means (Active-Sham) | 95% Confidence interval | P-value |
|---|---|---|---|---|---|
| | Sham (n=36) | Active (n=32) | | | |
| Mean (SD)<br>Median (IQR) | 0.21 (0.18)<br>0.15 (0.06, 0.33) | 0.22 (0.17)<br>0.17(0.07,0.36) | 0.01 | -0.07 to 0.09 | 0.78 |
| Adjusted for baseline salivary flow and centre (n=68) | | | -0.0009 | -0.08 to 0.08 | 0.98 |
| Adjusted for baseline, centre, age, gender, type of radiotherapy, years since radiotherapy completion, number of residual salivary glands (n=64) | | | -0.012 | -0.10 to 0.08 | 0.78 |

Table 4 Results from analysis of secondary outcome EORTC H&N35 over time (mixed effects ordinal models): pre-specified single-item of dry mouth, sticky saliva, cough score between randomised groups

| | Odds ratio (Active - Sham) | 95% Confidence interval | P-value |
|---|---|---|---|
| Dry mouth score | | | |
| Adjusted for baseline and visit (n=77) | 0.41 | 0.14 to1.21 | 0.106 |
| Adjusted for baseline, visit and centre (n=77) | 0.41 | 0.14 to 1.22 | 0.109 |
| Adjusted for baseline, time, centre, age, gender, Type of radiotherapy, years since radiotherapy completion, Number of residual salivary glands, (n=73) | 0.37 | 0.14 to 0.97 | 0.043 |
| Adjusted for baseline including an interaction with visit (n=77) | P-value for interaction with visit: 0.261 | | |
| Sticky saliva score | | | |
| Adjusted for baseline and visit (n=76) | 1.54 | 0.67 to 3.56 | 0.312 |
| Adjusted for baseline, visit and centre (n=76) | 1.54 | 0.67 to 3.57 | 0.312 |
| Adjusted for baseline, time, centre, age, gender, Type of radiotherapy, years since radiotherapy completion, Number of residual salivary glands, (n=72) | 1.35 | 0.57 to 3.22 | 0.493 |
| Adjusted for baseline including an interaction with visit (n=76) | P-value for interaction with visit: 0.848 | | |
| Cough score | | | |
| Adjusted for baseline and visit (n=77) | 0.67 | 0.26 to 1.74 | 0.408 |
| Adjusted for baseline, visit and centre (n=77) | 0.67 | 0.26 to 1.74 | 0.408 |
| Adjusted for baseline, time, centre, age, gender, Type of radiotherapy, years since radiotherapy completion, Number of residual salivary glands, (n=73) | 0.68 | 0.35 to 1.87 | 0.454 |
| Adjusted for baseline including an interaction with visit (n=77) | P-value for interaction with visit: 0.147 | | |