TITLE: Radiotherapy induced xerostomia: a randomised, double-blind, controlled trial of Visco-ease oral spray versus placebo in head and neck cancer patients

RUNNING TITLE: Visco-ease oral spray Vs placebo in xerostomia

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ADDITIONAL INFORMATION

Availability of data and material

The authors vouch for the accuracy and completeness of the data and its analysis and for adherence to the study protocol. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for

publication. The data was managed and analysed by the Robertson Centre of Biostatistics, University of Glasgow. Review of the data by the journal is welcome. Throughout the study, monitoring visits by the sponsor were made to the study site to confirm compliance with the study requirements.

Conflicts of interest

Authors A McLean, S Porteous and S Clark are employees and shareholders of Lamellar Biomedical Limited.

Lamellar Biomedical own the intellectual property rights to Lamellasome™ technology with the aim of commercialising Visco-ease and other lamellar body mimetics.

Dr Claire Paterson and the remaining authors have no conflicts of interest to declare and had full access to all of the primary data.

Funding

The study was funded by Lamellar Biomedical Limited.

Authors' contributions

The study idea was conceived and designed by CP, BC, RJ, AMcL, SP, SC and MCT. Statistical design and analysis was carried out by RY and CMM. Data management and analysis was overseen by SK. All authors contributed to acquisition of the data and interpreted the data. CP and MCT drafted the manuscript. All authors critically revised the manuscript.

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Radiotherapy induced xerostomia: a randomised, double-blind, controlled trial of Visco-ease oral spray versus placebo in head and neck cancer patients

ABSTRACT

Background

Radiotherapy induced xerostomia (RIX) is a common and untreatable side effect of head and neck (H&N) radiotherapy (RT).

Visco-ease is a novel product made from lamellar body mimetics which reduces the viscosity of saliva *ex-vivo*.

The purpose of this 1st-in-man study was to evaluate safety and effectiveness of Visco-ease mouth spray in the treatment of RIX.

Methods

43 patients with H&N cancer were randomised to receive Visco-ease or placebo oral spray. The Groningen Radiotherapy Induced Xerostomia (GRIX) questionnaire was completed weekly. The primary endpoint was change in GRIX score from baseline to end of treatment.

Results

There was no difference in GRIX scores between the two groups.

There were no device related SAEs in either group.

Conclusion

Visco-ease oral spray was safe and tolerable but was no better than placebo in reducing RIX in patients undergoing RT or CRT for H&N cancer as currently formulated.

Keywords

Radiotherapy Induced Xerostomia, Visco-ease, LMS-611, GRIX, Head and Neck Cancer

Clinical Trial Registration

Clinicaltrials.gov ID: NCT02687087

ISRCTN No: 44528835

INTRODUCTION

Radiotherapy (RT) induced xerostomia (RIX) is the most commonly reported late and permanent side effect of RT for head and neck cancer (HNC)[1] and impairs patients' quality of life (QoL), [2,3] causing discomfort, taste alteration, speech and swallowing difficulties and dental caries. [4]

Despite advances in radiation technology, clinically significant xerostomia affects around 40% of patients at 12 months post treatment. [5, 6] Furthermore, the changing epidemiology of HNC due to a rise in human papilloma virus (HPV) driven oropharyngeal cancer means patients are often younger[7] with a significantly improved response to treatment and overall survival, [8,9] therefore will live much longer with the consequences of treatment. [10, 11]

There is no effective treatment for RIX and a Cochrane review concluded that 'randomized controlled trials of topical interventions for dry mouth are required to provide evidence to guide clinical care'. [12]

Lamellar bodies have surface active properties and are an essential lubricant of the body's tissues, preventing mucosal surfaces from sticking to each other and sticky secretions, like thick saliva, from congesting the hollow organs.

Visco-ease, formerly known as LMS-611, is a multi-lipid mimetic of a naturally occurring lamellar body. Pre-clinical work suggested that Visco-ease may restore the thick, sticky saliva seen after RT to the H&N to more fluid saliva like that seen prior to RT. [13]

The purpose of this study was to evaluate the safety and effectiveness of Visco-ease mouth spray for the treatment of RIX in HNC patients. This was a first-in-man study of the device. In line with published recommendations [14] it was felt that patient reported outcomes were the most critical measures of effectiveness of Visco-ease. The validated Groningen Radiotherapy Induced Xerostomia (GRIX) questionnaire [15] was chosen to evaluate patient reported RIX during this study.

The primary endpoint was change in GRIX score from baseline to end of treatment and was compared between Visco-ease and placebo. Secondary objectives were to collect safety outcomes for each group and frequency of administration of the oral spray.

MATERIALS AND METHODS

Participants

Patients with HNC, who were scheduled to commence radical RT or chemoRT (CRT) as primary treatment, were recruited to this randomised, double-blind, and placebo controlled study.

Eligible patients were aged 18 years or older and were judged to be at high risk of RIX. Exclusion criteria included known pre-existing xerostomia, use of any investigational drug or product within 30 days, primary surgery for HNC and known allergies to egg, soya, or lanolin based products.

Randomisation and blinding

Patients were randomly assigned to receive Visco-ease or placebo (0.9% physiological saline) oral spray on a 2:1 basis. Independent randomisation was via an interactive web response system at The Robertson Centre for Biostatistics. Neither the patient nor investigators were informed of the treatment allocation. All treatment and placebo kits were presented in an identical manner to protect the study blinding.

Procedures

All patients received radical RT or CRT delivered with volumetric modulated arc therapy (VMAT). Gross tumour and the entirety of involved nodal levels received 65Gy/30# over 6 weeks. Prophylactic dose to areas considered at high risk of occult disease was 54Gy/30# over 6 weeks. Selection and delineation of target volumes was carried out according to international guidelines. [16] Cisplatin was delivered at 100mg/m^2 on day 1 and 22 of treatment for those receiving concurrent chemotherapy.

Patients were asked to use the oral spray (Visco-ease or placebo) as required but at least one spray, twice daily during the course of their RT, beginning on the first day

of treatment. They were instructed to deliver the spray under the tongue then to move the fluid around the mouth. The oral spray was initiated prior to the patients developing RIX to allow assessment of the tolerability of the product independent of the subsequent symptoms. Patients were assessed weekly during RT and concomitant medications and adverse events recorded. Patient reported xerostomia scores, using the GRIX questionnaire, were collected weekly. Subjects were also asked to keep a daily diary, recording the times and frequency of oral spray administration.

Statistical analysis

The primary endpoint for the study was change in GRIX score from baseline to week 6 of RT. Previous work demonstrated that the changes in GRIX scores over 6 weeks of RT were approximately normally distributed in untreated patients, with a mean of 65.2 and a standard deviation of 22.3. [13]

For the sample size calculation it was assumed that the mean change in the placebo group is 65 and the mean change in the treated group is 35. The standard deviation was assumed to be 23 in both groups. Group allocation was 2:1, with two subjects receiving Visco-ease spray for one subject receiving placebo.

The sample size calculation was based on comparing change in GRIX scores from baseline to week 6 of RT between the two groups using a two-sided two sample t-test, with significance level 0.05. The number of subjects required to achieve a power of 90% was 30, 20 subjects in the group receiving Visco-ease and 10 in the placebo group. The sample size calculation was carried out using Proc Power in SAS

9.3. To allow for a dropout rate of 25%, 41 subjects were required, 27 randomised to the group receiving Visco-ease and 14 to the placebo group.

Baseline characteristics were summarised overall and for each treatment group using mean, standard deviation (SD), minimum and maximum for continuous variables, and using counts and percentages for categorical variables.

Statistical analysis of the treatment effect, on the primary outcome of change in GRIX scores from baseline to end of treatment, was assessed using linear regression adjusting for baseline GRIX score.

All analyses were performed using the statistical software platform R. [17]

RESULTS

Ethics approval and consent to participate

The protocol was approved by West of Scotland Research Ethics Committee 4, (15/WS/0281) and MHRA (CI/2015/0053). Written informed consent was obtained from all participants. The study was sponsored by NHS Greater Glasgow and Clyde. The study was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Participants

43 patients (15 in the placebo group and 28 in the Visco-ease group) were recruited to the study between March and December 2016 from 62 patients screened, see figure 1, CONSORT diagram

Baseline Demographics

Table 1 shows the patient and tumour characteristics and treatment details. The patient demographics appeared well balanced between the two groups. Mean age was 59 years, almost 90% of participants were male and all had SCC. Oropharynx was the most common subsite with 70.8% of tumours HPV-positive across both groups. The most notable imbalance between the groups was in tumour staging. A higher proportion of patients in the Visco-ease group had stage III or IV disease or higher T staging compared to the placebo group. The higher use of concurrent CRT in the Visco-ease group is likely to reflect this more advanced disease stage. During the course of the study, withdrawals from both groups meant that this imbalance in disease stage increased further.

Patient reported xerostomia scores

Weekly GRIX scores are shown in figure 2. Patient reported xerostomia increases throughout RT. There was no statistically significant difference (calculated using ANOVA) between each group for mean clinic GRIX score at any time point.

The change in GRIX scores from baseline to end of treatment were compared between the treatment groups using linear regression adjusting for baseline GRIX score. No relationship was found (effect = -1.26, CI -21.77 to 19.24, p-value = 0.90)

Frequency of oral spray administration

The number of sprays used each day is shown in figure 3 for each group.

The number of sprays used increases initially during RT but then decreases again towards the end of treatment.

S*afety endpoints*

The occurrence of 'at least possibly device related' serious adverse events (SAEs) were monitored throughout the study. No such episodes were recorded for either group.

The number of participants with 'at least one adverse event (AE) or SAE was compared between the 2 groups as shown in table 2. There was no statistically significant difference in percentage of participants with an AE or SAE between the 2 groups. The relatively high frequency of AEs and SAEs reflects the significant acute toxicity this group of patients experience with RT or CRT and was anticipated.

DISCUSSION

Patient characteristics are as expected for a cohort undergoing primary RT for HNC. Patient reported xerostomia scores increase during RT. Previous work demonstrated a mean increase in GRIX score of 65.2 during 6 weeks of RT.[13] In this study, the mean increase in the Visco-ease group was less at 41.6. What was unexpected, however, was a similar increase in GRIX scores in the placebo arm of only 41.5. Laboratory work has already demonstrated no efficacy of the placebo (physiological saline) on the visco-adhesive properties of RIX saliva. [13] The smaller-than-expected increase in GRIX scores in the placebo group may be due to the well recognised placebo effect.

It is also feasible that the subjective symptom of RIX was genuinely improved with the use of oral saline spray compared to no intervention. Our findings confirm the importance of including a placebo for comparison when investigating new treatments for RIX. Some previous studies assessing interventions for RIX have not included a placebo arm. [18,19] Had the placebo group not been included we may have assumed the smaller increase in GRIX scores observed compared to the historical controls was clinically significant as the scores were around 36% less than recorded previously in the same setting (41.6 Vs 65.2).

Comparison between GRIX scores in the placebo and Visco-ease groups failed to show a significant difference at any time point. In particular the primary efficacy endpoint of a 30-point reduction in the GRIX score with Visco-ease compared to placebo was not met. This is partly due to lower than anticipated GRIX scores in the placebo group as discussed above. Furthermore, 4 patients (1 receiving Visco-ease and 3 placebo) did not develop RIX (as defined by not reaching a GRIX score of 30 or more at any point during the study) making it impossible for their scores to meet the primary efficacy endpoint.

The documented use of oral spray shows an increase in number of sprays used during the course RT with a reduction in use over the final 1-2 weeks of treatment. As no formal evaluation was made of compliance it is unclear if the documented frequency of use demonstrated true compliance with the oral spray or simply failure to record its use as time went on. Good compliance in the early weeks of use suggests good tolerability of the product.

No difference was demonstrated in the frequency of AEs or SAEs between the Visco-ease and placebo groups. No device related AEs were documented for either

group during the study. Therefore, this first-in- man study of Visco-ease has demonstrated a very safe toxicity profile.

It is disappointing that the study did not meet the primary efficacy endpoint of a significant reduction on RIX in the treatment Vs placebo group. Our results demonstrate some of the difficulties in carrying out a study of a new intervention for RIX. It is widely accepted that patient reported outcomes for xerostomia are the most important measure of judging success of an intervention for this symptom. [14] Physician reported scores or measures such as salivary flow do not necessarily demonstrate correlation with the symptom experienced by the patient. [1, 20] However, RIX is a very subjectively reported symptom, [14] making it a difficult metric to account for when designing a study such as this.

This study was carried out in patients currently receiving RT for HNC. RIX is often considered a late or chronic toxicity from RT to the H&N, but has also been demonstrated to occur as an acute toxicity, during treatment.[13, 21] The acute group of patients were chosen from a safety perspective as this medical device had not been tested in humans before and therefore it was important that we were able to monitor its effects closely in a group that were already attending hospital on a frequent (daily) basis. Patients who have completed RT generally attend as outpatients on a monthly or less frequent basis for ongoing assessment. Additional visits required for safety monitoring within the study were felt to be an unjustified burden in this group. It is likely, however, that the acute RIX patients comprise a group with a significantly higher symptom burden and poorer QoL than the chronic group. [22] Symptoms will include not only RIX but other acute toxicities seen with CRT and RT to the H&N such as mucositis, dysphagia, skin reaction, pain, anorexia,

weight loss, nausea and vomiting. It is likely that modifying one acute symptom will make little difference to the global QoL experienced by the patient, as overall, that QoL remains much poorer than at baseline. Now that the safety profile of Visco-ease has been demonstrated, further studies will be carried out in post-RT patients with established RIX, who are likely to have much more stable symptoms. As a result Visco-ease may demonstrate efficacy in the chronic RIX population and this area will be the focus of future work.

During randomisation, no stratification was made for any baseline patient, tumour or treatment characteristic, which produced a tendency for patients in the Visco-ease group to have Stage III and IV cancer and greater frequency of CRT. Unfortunately, given the nature of withdrawals during the study these imbalances were even more pronounced at the end of treatment. Higher stage disease will inevitably result in larger irradiated volumes being treated to a higher dose. Concurrent CRT is well known to cause increased toxicity compared to RT alone. [23, 24] It seems likely therefore that the Visco-ease group will have experienced a higher symptom burden than the placebo group which may have skewed the results. Stratification for all potentially confounding variables in this study (patient age, concomitant medication, smoking/alcohol history, tumour stage and treatment: RT Vs chemoRT) would have meant that a larger sample size were required. This was felt to be inappropriate by the investigators given the 1st-in-man nature of the study. Exploratory, post hoc analyses were carried out after these initial results were examined and the difficulties described above were considered.

All patients who failed to reach a GRIX clinic score of 30 or more were excluded. Multi-variate regression was used to identify the factors which had the greatest

influence on GRIX scores. These were tumour staging, concurrent CRT, MST use and study treatment. When using the restricted population, after adjusting for the potentially confounding covariates there appeared to be a positive effect of Visco-ease compared to placebo in reducing GRIX scores. This supplementary data will only be used to inform the design of future clinical studies and not to make any efficacy claims. It does however suggest that a signal may be detected with an appropriately designed study and this is worth progressing. An alternative formulation of Visco-ease e.g. oral rinse rather than spray is also under consideration for future studies.

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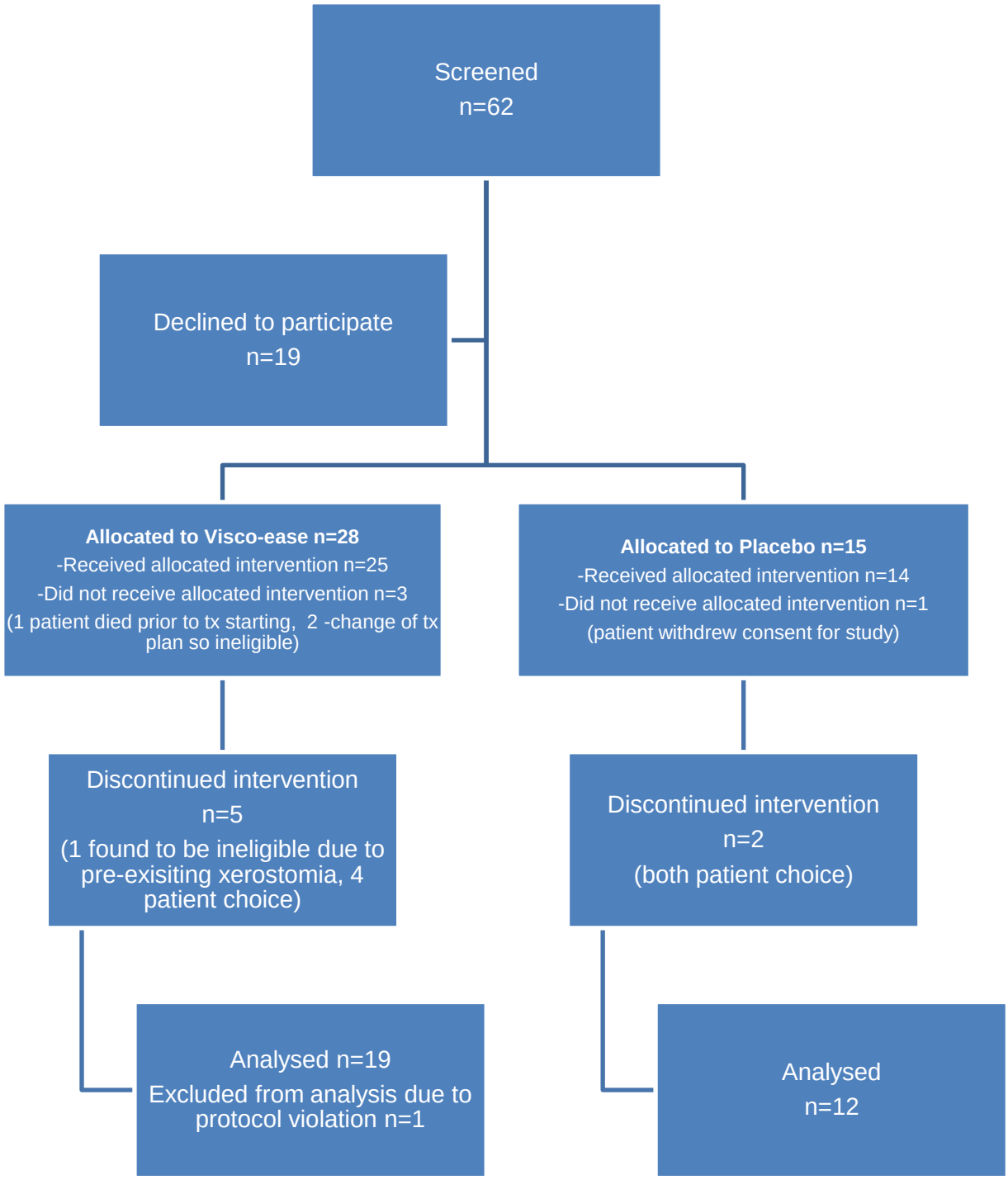
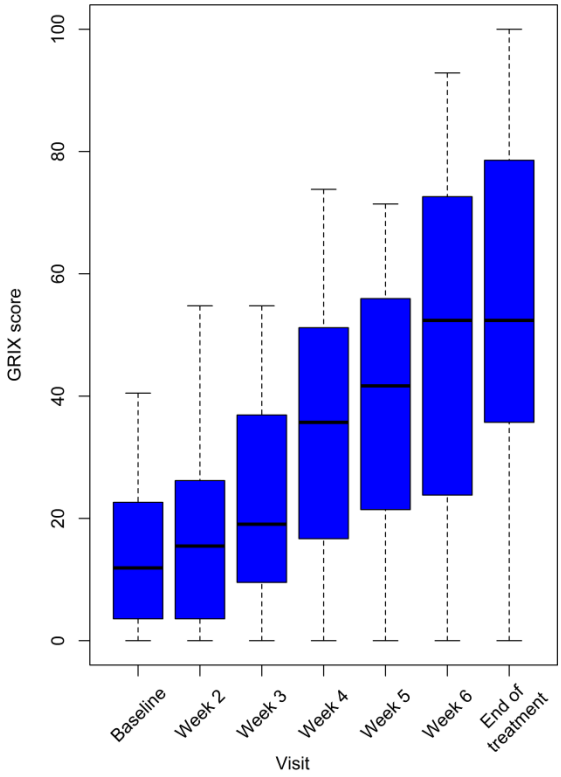
FIGURE LEGENDS

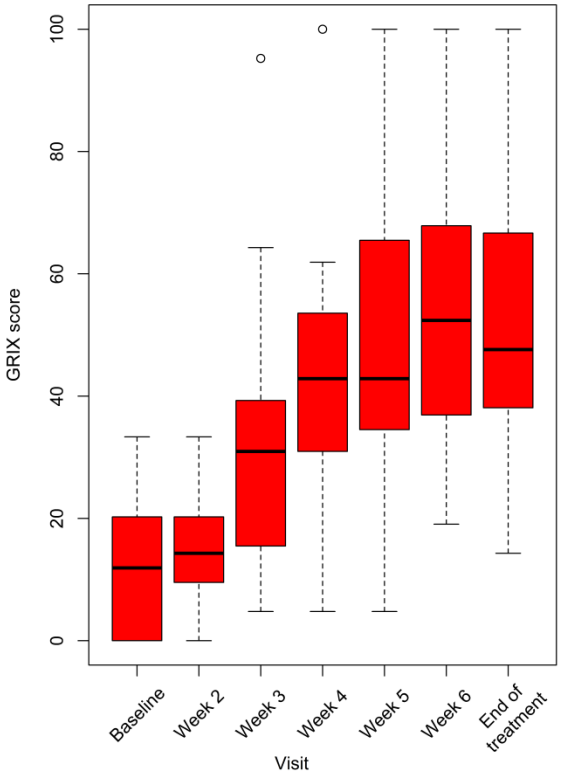
Figure 1, Trial Profile, CONSORT flow diagram

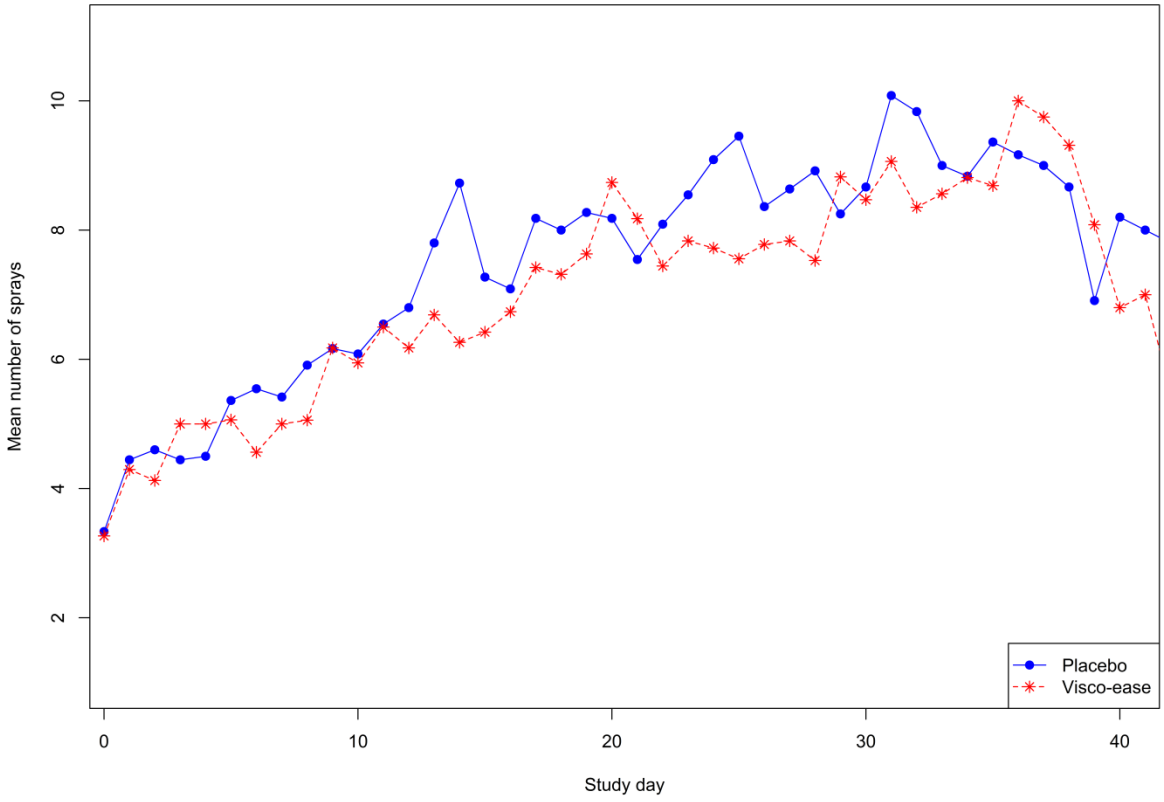
Figure 2, Weekly GRIX Clinic Scores, blue = placebo, red = Visco-ease

Figure 3 Number of Sprays Used per Day


Screened
n=62
Declined to participate
n=19
Allocated to Visco-ease n=28
-Received allocated intervention n=25
-Did not receive allocated intervention n=3
(1 patient died prior to tx starting, 2 -change of tx plan so ineligible)
Allocated to Placebo n=15
-Received allocated intervention n=14
-Did not receive allocated intervention n=1
(patient withdrew consent for study)
Discontinued intervention
n=5
(1 found to be ineligible due to pre-exisiting xerostomia, 4 patient choice)
Discontinued intervention
n=2
(both patient choice)
Analysed n=19
Excluded from analysis due to protocol violation n=1
Analysed
n=12


GRIX score
0
20
40
60
80
100
Baseline
Week 2
Week 3
Week 4
Week 5
Week 6
End of treatment
Visit


GRIX score
0
20
40
60
80
100
Baseline
Week 2
Week 3
Week 4
Week 5
Week 6
End of treatment
Visit


Mean number of sprays
2
4
6
8
10
0
10
20
30
40
Study day
Placebo
Visco-ease

		Placebo (n=14) Number (%)	Visco-ease (n=25) Number (%)
Age (years)	Mean Range	61.6 50.5 – 78.2	58.0 41.3 – 70.3
Gender	Male Female	13 (92.9%) 1 (7.1%)	22 (88.0%) 3 (12.0%)
Sub Site	Oropharynx Larynx Hypopharynx Nasopharynx UKP	9 (64.3%) 3 (21.4%) 1 (7.1%) 1 (7.1%) 0 (0%)	15 (60.0%) 5 (20.0%) 2 (8.0%) 0 (0%) 3 (12.0%)
Pathology	SCC	14	25
T staging	T0-T1-T2 T3-T4	12 (85.7%) 2 (14.3%)	20 (80.0%) 5 (20.0%)
Stage	I-II III-IV	4 (28.6%) 10 (71.4%)	3 (12.0 %) 22 (88.0%)
Concurrent CRT	Yes No	7 (50.0%) 7 (50.0%)	17 (68.0%) 8 (32.0%)

Table 1 Baseline Demographics for APT

Event	Placebo (n=14)	Visco-ease (n=25)	p-value (Fishers exact test)
Non serious AE	4 (28.6%)	6 (24.0%)	1.000
SAE	6(42.9%)	14 (56.0%)	0.5145

Table 2. Comparison between treatment groups of subjects with at least 1 AE or SAEs (APT)