Poster P008

Results of a phase 1 open-label, dose escalation study of gene therapy with AAV2-hAQP1 as treatment for radiation induced xerostomia and parotid gland hypofunction

Michael Brennan[1], Michael Passineau[2], Deborah Saunders[3], Herve Sroussi[4], Dyani Gaudilliere[5], Arthur Fernandez[2], Jun Liu[2], Nathalie Dubois[2], Robert Zeldin[2]

[1]Atrium Health, NC, USA [2]MeiraGTx [3]Health Science North, Ontario, CA [4]Brigham and Women's Hospital MA, USA [5]Stanford University, CA, USA

1. Introduction

In radiation-induced xerostomia, the normal architecture and function of salivary glands are significantly disrupted or destroyed.

AAV2-hAQP1 vector expresses the human Aquaporin 1 (hAQP1) gene delivered using the AAV2 capsid. When hAQP1 is expressed in cells of the disrupted glands, the cells become permeable to water. Water flows down the hydrostatic pressure gradient through the salivary duct and into the mouth.

2. Design and Methods

In this study, AAV2-hAQP1, at doses ranging from 1 × 10^{11} vg/gland to 3 × 10^{12} vg/gland, was administered to one (unilateral) or both (bilateral) parotid glands via intraoral, retroductal cannulation of Stensen's duct. Key inclusion criteria for study participants were a history of head and neck cancer, a minimum of five years since final radiotherapy treatment (two+ years if HPV+), the presence of grade 2/3 late xerostomia, no evidence of cancer recurrence or second primary, and abnormal parotid gland function. Key exclusion criteria were a history of autoimmune disease affecting the salivary glands and a hemoglobin A1c greater than 7%.

Safety parameters included assessments of adverse events, physical examination observations, clinical laboratory results, and electrocardiogram findings. Efficacy assessments included participant completion of the Xerostomia-specific Questionnaire (XQ), the MD Anderson Symptom Inventory for head and neck cancer (MDASI-HN), and the Global Rate of Change Questionnaire (GRCQ), as well as measurement of saliva flow rates. The XQ is a questionnaire consisting of eight symptom-specific questions that the participant rates from 0 (not present) to 10 (worst possible). The sum of all ratings (0-80) provides an overall measure of symptom burden. An 8-point improvement is considered clinically meaningful. The MDASI-HN is a validated symptom inventory of 28 items that covers many aspects of head and neck cancer. Question #10, the "Dry Mouth" question (MDASI-DM), whose value ranges from 0 to 10, is the only question that directly addresses xerostomia. Therefore, the responses to the MDASI-DM were analyzed and reported separately. The GRCQ is a tool used to assess patient-perceived changes and has been adapted for xerostomia. The GRCQ Symptom Change Module (GRCQ-S) first asks the participant if their dry mouth is "better", "worse", or "about the same" following treatment. If the participant reports "better" or "worse," they are then asked to rate the degree of change on a scale from 1 to 7, with 1 being the smallest change and 7 being the greatest change. A GRCQ-S score of 2 or above is important to the patient. To evaluate the biologic activity of AAV2-hAQP1, whole saliva flow rates were assessed.

For each efficacy outcome, the Change from baseline (CFB) and percent change from baseline (%CFB) were modeled using a Mixed Model of Repeated Measures (MMRM), adjusted for baseline value and actual dose concentration.

3. Safety Results

A total of 24 adults were enrolled in the study, with twelve participants treated unilaterally and twelve treated bilaterally.

- AAV2-hAQP1 was safe and well-tolerated at all dose levels, with no treatment-related serious adverse events (SAEs) and no treatment-emergent adverse events (TEAEs) leading to study discontinuation, or dose-limiting toxicity.
- TEAEs of special interest were reported for three participants and included oral disorder, salivary gland pain, and injection site pain. All were grade 1 in intensity.
- Six participants had at least one TEAE assessed by the investigator as treatment-related. None of the preferred terms was reported in more than one participant. All treatment-related TEAEs were grade 1 in intensity and resolved without sequelae.

No safety signals emerged from the review of vital signs parameters, results of oral and physical examinations, laboratory parameters, or ECG interpretation.

4. Efficacy Results – Patient Reported Xerostomia Symptoms

Figure 1. XQ Total Score LS Mean Change from Baseline (95% CI)

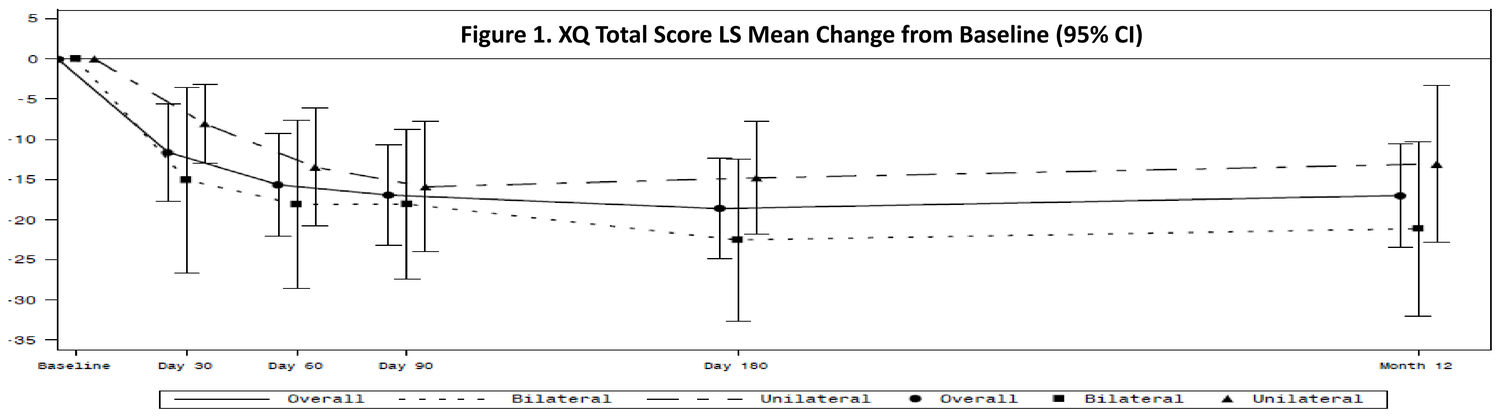


Figure 2. MDASI-DM LS Mean Change from Baseline (95% CI)

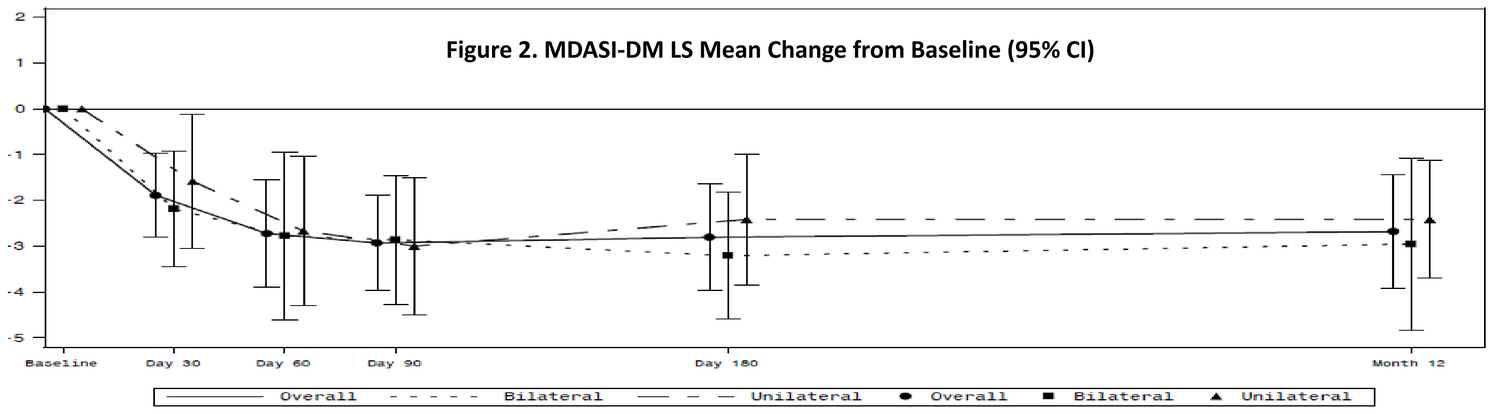
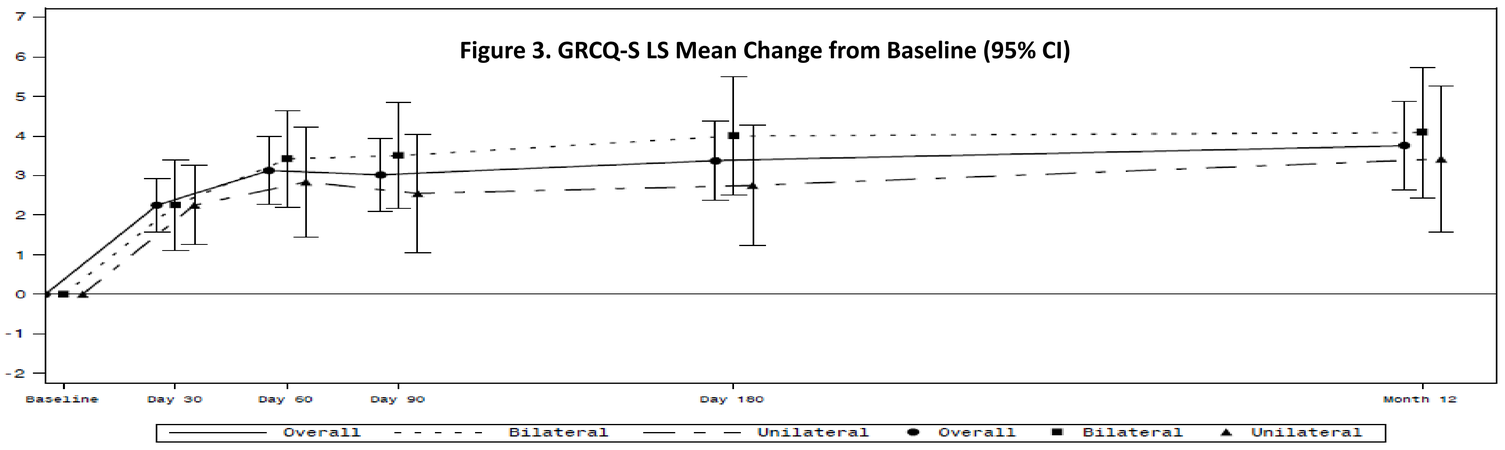


Figure 3. GRCQ-S LS Mean Change from Baseline (95% CI)



The MMRM estimated mean CFB in XQ Total Scores by visit and the associated 95% confidence interval (CI) limits are plotted in Figure 1. The mean CFB at Month 12 was -13.0 for unilaterally treated participants and -21.1 for bilaterally treated participants. XQ Total Scores for the unilateral and bilateral cohorts, and for all cohorts combined showed statistically significant changes relative to baseline by the Day 30 visit that were maintained through the Month 12 visit. At Month 12, 16 of the 24 participants (67%) had an improvement of ≥8 points in XQ Total Score, signifying clinically meaningful changes.

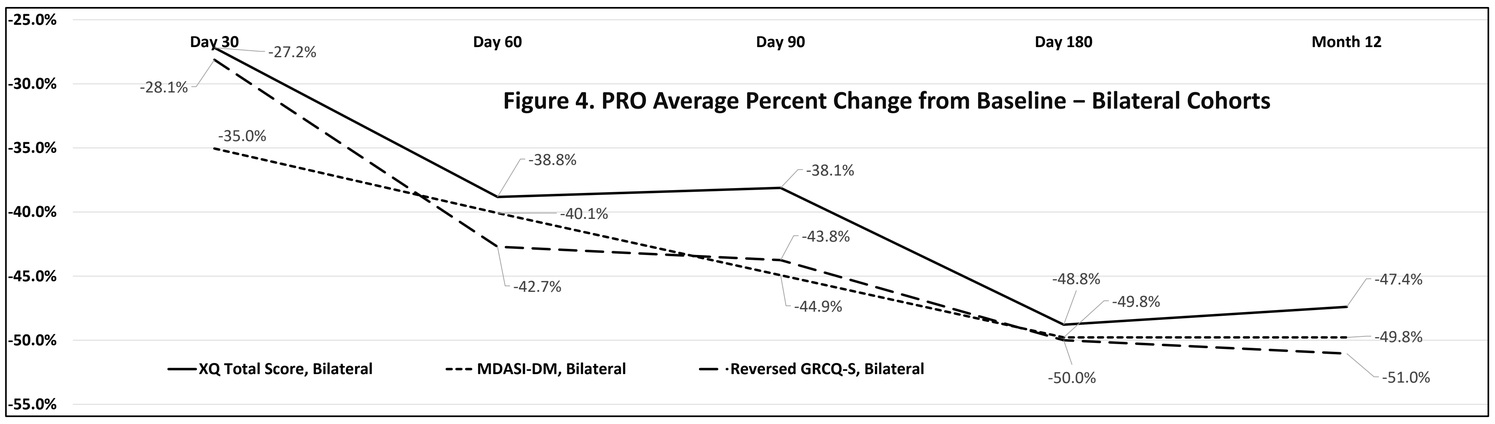
The MMRM estimated mean CFB in MDASI-DM scores by visit and associated 95% CI limits are plotted in Figure 2. The improvement in scores was statistically significant at the Day 30 visit for the unilateral and bilateral cohorts and for all cohorts combined and was maintained through Month 12.

The MMRM estimated mean GRCQ-S scores by visit and associated 95% CI limits are plotted in Figure 3. The mean change in GRCQ-S scores was +3.4 for unilaterally treated and +4.1 for bilaterally treated participants at Month 12. The estimated mean CFB for GRCQ-S scores was statistically significant starting at the Day 30 visit and was maintained through Month 12. At the Month 12 visit, 18 of the 24 participants reported important improvement in xerostomia symptoms relative to baseline (i.e., ≥2 points).

The MMRM results for %CFB exhibit patterns and levels of statistical significance similar to those of the PRO changes. For the XQ Total Score, MDASI-DM score, and GRCQ-S score, the %CFB at Month12 were -47.4%, -49.8%, and -51.0%, respectively.

While the three PRO tools measure different aspects of a patient's subjective experience of xerostomia, they showed similar patterns of improvement over the 12-month post-treatment period. When compared using the %CFB (bilateral cohorts), the consistency in the magnitude of change across instruments, as shown in Figure 4, underscores the positive impact of AAV2-hAQP1 treatment on xerostomia symptoms and quality of life.

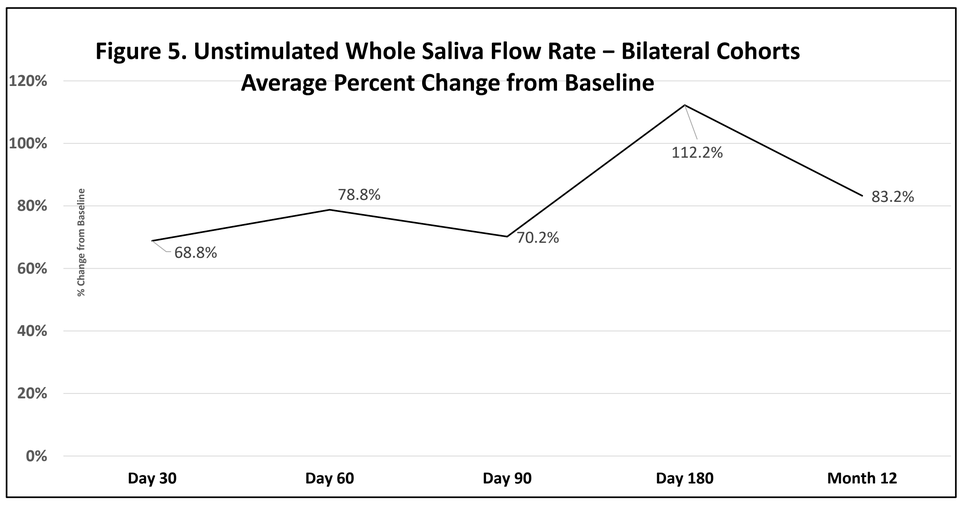
Figure 4. PRO Average Percent Change from Baseline – Bilateral Cohorts



5. Efficacy Results – Saliva Flow Rate

In bilaterally treated participants, the average percent increase in unstimulated whole saliva flow rate at Month 12 post-treatment relative to baseline was 83.2% ($p<0.04$, Figure 5).

Figure 5. Unstimulated Whole Saliva Flow Rate – Bilateral Cohorts
Average Percent Change from Baseline



6. Conclusions

Treatment with AAV2-hAQP1 was safe, resulted in important improvements in symptoms of radiation-induced xerostomia, and increased unstimulated whole saliva flow rate. Based on these promising results, a Phase 2 study has been initiated (NCT05926765).

7. References

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