MEIRAGTx

Corporate Presentation

October 2026

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding our product development, our ability to manufacture product candidates, potential milestone payments and the achievement of such milestones, and our pre-clinical and clinical data, reporting of such data and the timing of results of data, as well as statements that include the words “expect,” “intend,” “plan,” “believe,” “project,” “forecast,” “estimate,” “may,” “should,” “anticipate” and similar statements of a future or forward-looking nature. These forward-looking statements are based on management’s current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, our incurrence of significant losses; any inability to achieve or maintain profitability, raise additional capital, repay our debt obligations, identify additional and develop existing product candidates, successfully execute strategic transactions or priorities, bring product candidates to market, expansion of our manufacturing facilities and processes, successfully enroll patients in and complete clinical trials, accurately predict growth assumptions, recognize benefits of any orphan drug or rare pediatric disease designations, retain key personnel or attract qualified employees, or incur expected levels of operating expenses; the impact of pandemics, epidemics or outbreaks of infectious diseases on the status, enrollment, timing and results of our clinical trials and on our business, results of operations and financial condition; failure of early data to predict eventual outcomes; failure to obtain FDA or other regulatory approval for product candidates within expected time frames or at all; the novel nature and impact of negative public opinion of gene therapy; failure to comply with ongoing regulatory obligations; contamination or shortage of raw materials or other manufacturing issues; changes in healthcare laws; risks associated with our international operations; significant competition in the pharmaceutical and biotechnology industries; dependence on third parties; risks related to intellectual property; changes in tax policy or treatment; our ability to utilize our loss and tax credit carryforwards; litigation risks; and the other important factors discussed under the caption “Risk Factors” in our most recent quarterly report on Form 10-Q or annual report on Form 10-K or subsequent 8-K reports, as filed with the Securities and Exchange Commission. These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management’s estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, unless required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Thus, one should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation. Unless otherwise stated or the context otherwise requires, the information herein is as of October 14, 2026.

Company Overview

MEIRAGTx

MeiraGTx: late-stage clinical pipeline and comprehensive end-to-end capabilities & technologies in genetic medicine

Diverse Program Pipeline

Broad pipeline across neuro, salivary gland, and ophthalmology

4 pivotal and BLA ready programs:

- Radiation-induced xerostomia
- X-linked retinitis pigmentosa
- Parkinson's disease
- AIPL1 retinal dystrophy (Eli Lilly)

Diverse preclinical pipeline:

- ALS, intractable neuropathic pain, obesity & diabetes, large ophthalmology indications such as Stargardt's, wet and dry AMD

Unlimited potential of transformative Riboswitch-small molecule control of therapeutic protein in vivo production

End-to-End GMP Manufacturing

In-house manufacturing and industry-leading process

- 2 cGMP viral vector manufacturing facilities
- QC facility for release and stability
- In-house Fill & Finish, warehouse and supply chain
- Dedicated MSAT facility
- Commercial ready Platform Process and QC

Commercial licenses for both viral vector production as well as QC

Next-Generation Vector Optimization

Improved potency & safety, lower dose and lower COGS

- >250k promoter library
- AI enhanced promoter optimization
- Proprietary intravitreal capsids
- Capsid development: muscle, CNS
- Human organoids

Improve potency up to 3 to 4 logs, reducing dose 3-4 logs, reducing Cost of Goods and improving safety

Transformative *in vivo* production Technology

Proprietary Riboswitch platform for precise control of therapeutic proteins

***in vivo* production of physiological, efficacious levels of any therapeutic protein via bespoke small molecule oral dosing**

- **Gene agnostic**: multiple antibodies, peptides, hormones, nucleases, cell therapy validated in animal models
- **Delivery agnostic:** AAV, Lentivirus and CRISPR all demonstrated equivalent tight control
- **Leptin**: first into the clinic, 2026
- hGH, PTH, EPO, Antibodies, Cell therapy

Broad Pipeline of Transformative Genetic Medicines

Advanced clinical programs across multiple therapeutic areas

Product	Indication	Preclinical	Phase 1	Phase 2	Phase 3 / Registrational
Salivary Gland					
AAV-AQP1	**Radiation-induced xerostomia**	*Breakthrough Designation, RMAT, Orphan*			
	Sjögren's disease		*IND ready*		
	PSMA radioligand xerostomia prophylaxis and treatment				
Ophthalmology					
Botaretigene sparoparvovec	**X-linked RP (RPGR)**	*PRIME, Fast Track, Orphan Drug*			
AAV-AIPL1	**LCA4 congenital blindness** Lilly	*RPDD, Orphan Drug, MHRA Specials License*			
AAV-ABCA4	**Stargardt's disease**				
AAV-VEGFR2	**Wet AMD**				
Undisclosed	**Dry AMD/GA**				
BBS10	**Bardet-Biedl syndrome**	*RPDD, Orphan Drug*	*Developed under MHRA Specials License*		
Neurodegenerative Disease					
AAV-GAD[1]	**Parkinson's disease**	*RMAT*			*Phase 3 ready*
AAV-UPF1, AAV-CNTFR	**ALS**				
Riboswitch Regulated Therapies					
RiboLeptin	**Lipodystrophies**				
Undisclosed	**Intractable neuropathic pain**				
GLP-1, GIP, incretin combinations	**Obesity/MASH/Metabolic Disease**				
Ribo-CAR-T	**Oncology, autoimmune disease**				
Genetic Obesity					
AAV-BDNF[1]	**MC4R/BDNF genetic obesity**				

[1] Joint venture with Hologen AI (see press release here)

Unique end-to-end, in-house GMP manufacturing infrastructure and production platform process, scalable and flexible, fit for clinical & commercial supply

End-to-end internal manufacturing infrastructure, capabilities and production process

Best in class, fully end-to end internal capabilities: Two flexible & scalable cGMP vector production facilities, London, UK and Shannon, Ireland; cGMP QC facility for release and stability; fill and finish; dedicated MSAT process development facility

Commercial licenses in Ireland and UK for viral vector production and QC

Proprietary Commercial Ready Manufacturing Process at IND: Reduces AAV clinical development timeline by 2-3 years, from IND to commercial and allows faster move to pivotal with expedited time to market

Global regulatory relationships and extensive experience from pre-IND through BLA/commercial

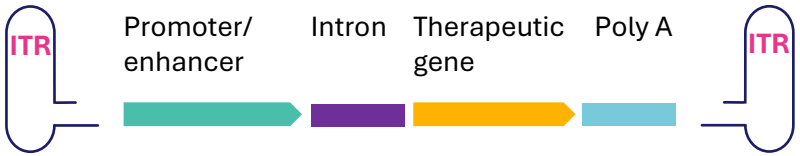
Commercial grade manufacturing with scalable and flexible capacity, clinical and commercial supply

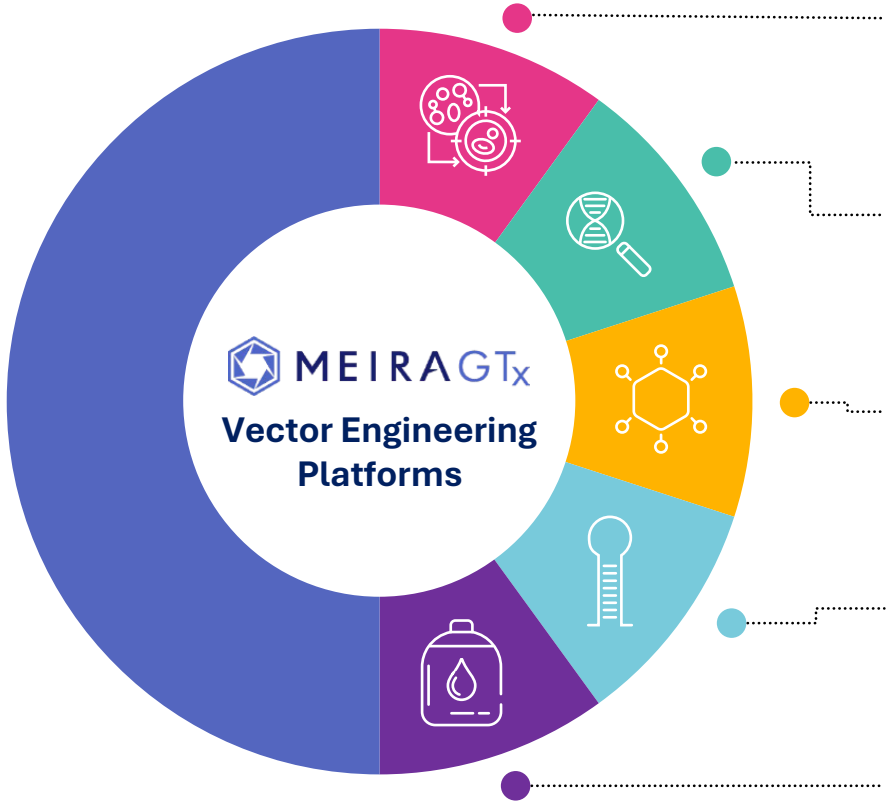
Comprehensive vector engineering technologies

Potency & safety optimization and precise control of gene expression

In-house vector engineering platforms

Extensive in-house vectorology capabilities addressing each element of the vector genome sequence





Promoter engineering & discovery

>250k promoter library

Combine rational design, massive high throughput screening, and AI to optimize proprietary promoters

Gene sequence optimization

Intron/exon configuration, poly A, translation efficiency, mRNA stability, reduced immunogenicity

Capsid design

Proprietary capsids with high transduction efficiency, including novel intravitreal capsids targeting back or front of the eye – screened directly in NHPs; muscle and CNS capsids

Riboswitch gene regulation

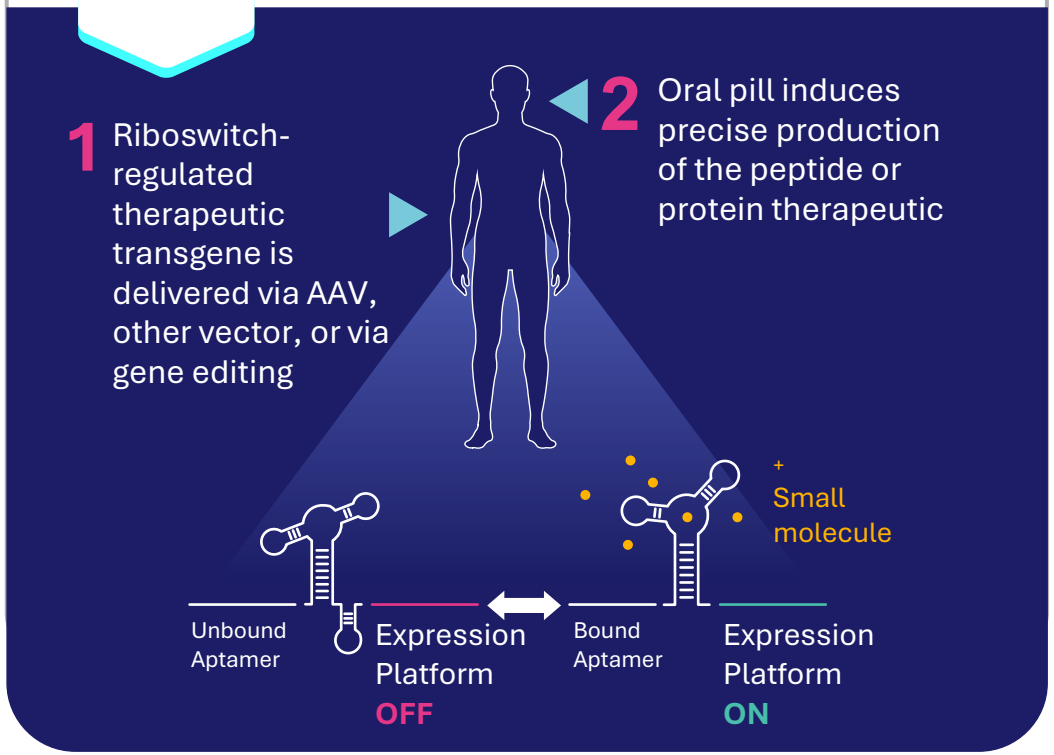
Precise dose responsive control of *in vivo* therapeutic protein production with bespoke oral small molecule inducers

Manufacturability

Optimal plasmid design and vector sequence optimization for industry-leading high yield and full/empty ratio

Riboswitch platform: precise *in vivo* production of therapeutic proteins using oral small molecule inducers

Riboswitch technology enables unprecedented precise *in vivo* delivery of biologic therapeutics with orally administered inducers



Riboswitch technology can be applied across many therapeutic areas and modalities, providing titratable control of gene expression with an oral pill

- Vectorized biologics
- Cell Therapy
- Gene Editing
- Short-lived hormones & peptides
- Control CNS & PNS Therapies
- Control Ocular Therapies

A broad range of therapeutic proteins encoded by Riboswitch-containing transgenes show tight control via oral small molecule dosing, *in vivo*

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (eye)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2
- Anti-IL4Ra
- Anti-Myostatin

Cell Therapy

RiboCAR:

- Anti-CD19
- Anti-PSMA
- Anti-mesothelin
- Anti-HER2
- Cytokines

- ProTcell (progenitor T cell) derived riboCAR-T

Therapeutic Hormones/Cytokines / Peptides

- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1, GIP, PYY, Glucagon, Amylin, Oxyntomodulin
- Myokines
- Adipokines e.g: leptin

Gene/RNA Editing Nucleases

- Cas9
- CasRx

Four pivotal stage programs in prevalent and rare indications

Radiation-Induced Xerostomia

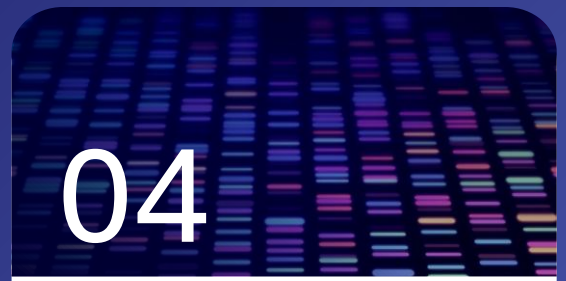
- Completed Enrollment of Pivotal Phase 2 study
- **Potential BLA filing mid 2027**
- Large patient population with no effective therapies available
- ‘Pipeline in a product’

X-Linked Retinitis Pigmentosa (RPGR)

- Completed Phase 3
- **BLA and MAA submissions planned 2026**
- MeiraGTx manufactures commercial product

AIPL1-Associated Congenital Blindness

- Developed under ‘specials’ license
- **Near term BLA and MAA filings– FDA and MHRA**
- Transformative effect - 11/11 blind to seeing children under 4 years
- Exclusively licensed to Lilly



Parkinson’s Disease

- Phase 3 ready
- **Potential BLA filing in 2028**
- Large patient population inadequately controlled by dopamine therapy

Strong industry partnerships

Lilly

In November 2025, MeiraGTx entered into a broad strategic collaboration with Eli Lilly to develop and commercialize genetic medicines in ophthalmology

MeiraGTx received $75 million in upfront cash, as well as up to $135 million in potential near-term milestone payments related to AAV-AIPL1.

MeiraGTx is also eligible to receive additional milestone payments and tiered royalties on licensed products.

Under the terms of the agreement, Lilly obtained:

- Worldwide exclusive rights to MeiraGTx's AAV-AIPL1 product for LCA4
- Exclusive license to certain MeiraGTx proprietary intravitreal capsids as well as certain proprietary promoters for use with up to five ocular disease targets
- A Right of First Negotiation (ROFN) to MeiraGTx's proprietary Riboswitch Technology in the field of gene editing in the eye

Link to press release

sanofi

In October 2023, MeiraGTx received a $30 million strategic investment from Sanofi through sale of 4 million ordinary shares at $7.50 per share

Sanofi received a Right of First Negotiation (ROFN) for MeiraGTx's phase 2 xerostomia program, as well as for the use of MeiraGTx's Riboswitch gene regulation technology in certain targets:

- Immunology and Inflammation (I&I), including IL-4 and IL-13
- GLP-1 and other gut peptides for metabolic disease and obesity
- Central Nervous System (CNS)

In August 2024, Sanofi made an additional $30 million equity investment in MeiraGTx as part of a $50 million offering of ordinary shares

Link to press release

HOLOGEN AI

MeiraGTx entered into a strategic collaboration with Hologen AI to expedite Phase 3 development of AAV-GAD and industrialize MeiraGTx's proprietary manufacturing process

- **MeiraGTx to receive $200 million in upfront cash consideration**
- MeiraGTx and Hologen formed a JV with an additional $230 million committed capital from Hologen to fund 100% of AAV-GAD program through to commercialization, as well as other potential pipeline products
- Hologen will also fund a portion of MeiraGTx's manufacturing operations and will own a minority stake in MeiraGTx's manufacturing subsidiary

Link to press release

Late-stage clinical programs

AAV-AQP1 for treatment of grade 2/3 xerostomia: Pivotal Study enrollment completed in 2Q 2026

Bota-vec for the treatment of X-Linked Retinitis Pigmentosa (XLRP): Phase 3 complete, BLA and MAA filing preparation under way

AAV-AIPL1 for treatment of LCA4: potential near-term path to regulatory approvals

AAV-GAD for treatment of Parkinson's Disease (Phase 3 ready)

MEIRAGTx

AAV-AQP1 for treatment of xerostomia - pivotal Phase 2 enrollment complete

Large patient population with no effective treatment options

Radiation-Induced Xerostomia (RIX)

Pivotal Phase 2 study completed enrollment in 2Q

Granted Breakthrough, RMAT and Orphan Drug designations

- **RIX is one of the most frequent complications of radiation treatment for head & neck cancer**
- **~200K patients in the US alone**
- **Large patient population with severe unmet need**

AAV-AQP1 Treatment:

Small dose delivered directly to salivary gland

In-office procedure

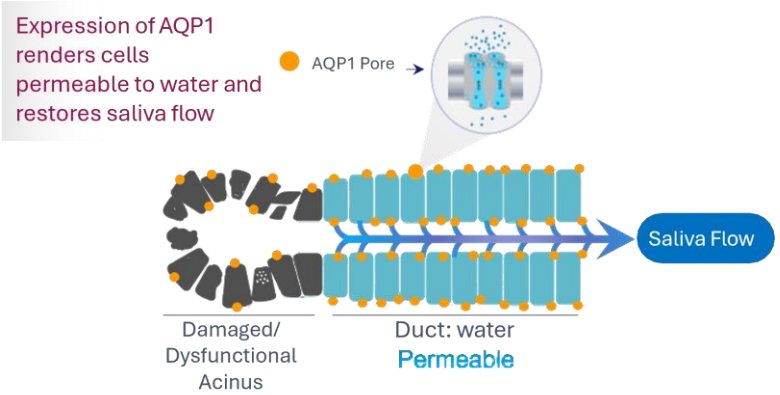
No general anesthesia

One-time therapy

Low cost of goods

MECHANISM OF ACTION

- Saliva-producing cells are vulnerable to Ionizing radiation used to treat head & neck cancer and PSMA radioligands
- Expression of the water channel Aquaporin 1 (AQP1) in the salivary gland duct allows water to flow into the salivary duct and out to the oral cavity to moisten the mouth



TRANSFORMATIVE CLINICAL IMPROVEMENTS

- Compelling Phase 1 data presented April 2026 with 24 patients - with magnitude of improvements unprecedented in this condition (see here)
- **Improvements across all efficacy endpoints considered 'unprecedented' and 'transformative' by KOLs**
- **Granted Breakthrough and RMAT designations; written alignment with FDA on path to BLA**
- **Pivotal Phase 2 enrollment complete**

PIPELINE IN A PRODUCT

- ☑ **Radiation-induced xerostomia**
- ☑ **Sjögren's disease**
- ☑ **Radioligand therapies (xerostomia is a dose limiting AE for PSMA radioligands)**
- ☑ **Prevention of radiation-induced or PSMA radioligand xerostomia**

MEIRAGTx

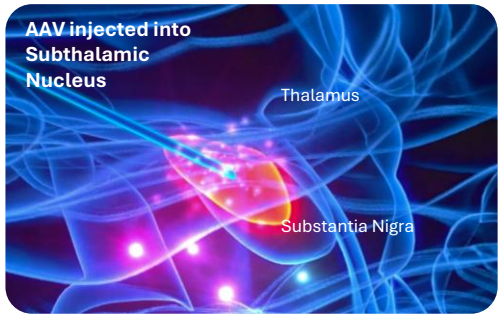
AAV-GAD for treatment of Parkinson's disease - Phase 3 ready

Meaningful clinical improvements with evidence of disease modification

The only CNS gene therapy program with two randomized, double-blind, sham surgery-controlled trials which met the prespecified primary endpoint

MECHANISM OF ACTION

- AAV-GAD delivers a functional copy of the Glutamic Acid Decarboxylase (GAD) gene locally to the sub-thalamic nucleus (STN)
- GAD converts glutamate (excitatory neurotransmitter) to GABA (inhibitory neurotransmitter) to alleviate PD-associated hyperexcitation of the STN



LARGE PATIENT POPULATION IN NEED OF EFFECTIVE TREATMENT

- ☑ **Small dose, local delivery – favorable safety & low COGS**
- ☑ **One-time treatment; brief surgical procedure with no general anesthesia**
- ☑ **No in-dwelling hardware**
- ☑ **Internally manufactured by MeiraGTx using commercial-ready process**

MEANINGFUL EFFICACY VS. SHAM SURGERY CONTROL

- 58 patients in 3 independent multicenter clinical studies were treated with AAV-GAD
- Generally safe and well tolerated in all doses tested, with no treatment-related SAEs
- **Phase 2 study met primary endpoint of UPDRS 3 motor score improvement vs. sham at 6 months; Improvements persisted at 12 months**
- **Evidence of disease modification – in collaboration with Hologen AI**
- Improvements in multiple secondary outcome measures

STATUS: PHASE 3 READY

- **Granted RMAT designation in 2025**
- **October 2024: positive data reported from AAV-GAD sham-controlled bridging study, using higher dose and material manufactured in-house by MeiraGTx:**
  - **Significant improvement of 18 points over baseline in UPDRS Part 3 in the high dose group at 26 weeks**
  - Significant improvement in quality of life measures (PDQ-39), in both the high and low dose groups at 26 weeks

AAV-AIPL1 for treatment of LCA4 congenital blindness

Restoring vision in children who are born legally blind

AIPL1 Retinal Dystrophy (LCA4)[1]

- **Children with AIPL1-associated retinal dystrophy are blind from birth and by age 4, retinal degeneration is complete and irreversible**
- **Path to Marketing Authorization under Exceptional Circumstances**

[1] Partnered with Eli Lilly

MECHANISM OF ACTION

- AAV8-AIPL1 delivers the wild-type human AIPL1 gene under control of a photoreceptor-specific rhodopsin kinase promoter, hRK
- AAV-AIPL1 is administered subretinally as a one-time treatment

TRANSFORMATIVE CLINICAL IMPROVEMENTS

- 11 children have been successfully treated in the UK under an MHRA Specials License – 4 unilaterally & 7 bilaterally
- There were no safety concerns in either of the patient groups
- **Efficacy has been demonstrated in all 11 patients: 100% of treated children who were legally blind from birth regained visual acuity, with benefits seen from 1 month following treatment**
- In the unilateral treatment group, durable efficacy has been shown **up to 4 years** (the longest follow up point)

POTENTIAL PATH TO MARKETING AUTHORIZATION

The company presented data produced under the Specials License to the MHRA and FDA:

- MeiraGTx was advised by MHRA to file for 'Marketing Authorization Under Exceptional Circumstances. No further clinical data was requested
- In addition, a CMC package appropriate for such a rare condition was agreed
- AAV-AIPL1 for LCA4 received rare pediatric disease designation (RPDD) from FDA - approval may result in a Priority Review Voucher (PRV)

MEIRAGTx

AAV-AQP1: a pipeline in a product for treatment of xerostomia

Pivotal Phase 2 Study enrollment complete in radiation induced xerostomia

Granted RMAT and Orphan Drug designations

Alignment with FDA on pivotal clinical trial design and CMC for BLA filing

Pipeline in a product: multiple prevalent indications with high unmet need

01

Radiation-induced xerostomia

- Pivotal Phase 2 enrollment complete
- >170,000 patients with grade 2/3 xerostomia in US alone
- Large ex-US incidence and prevalence
- >80% inadequately controlled by current SOC

02

Xerostomia associated with Radioligand Therapy

- Xerostomia is the most common AE of PSMA radioligand therapy, and a dose-limiting toxicity
- AAV-AQP1 has the potential to treat xerostomia in this rapidly growing market as a treatment, but more importantly pretreatment prophylaxis

03

Sjögren's-related xerostomia

- Prevalent autoimmune condition disrupting tear- and saliva-producing glands
- No effective treatments for Sjögren's-related xerostomia
- >550,000 Sjögren's patients with grade 2/3 xerostomia in the US alone

04

Prevention of radiation-induced xerostomia

- Preclinical data suggest that treatment with AAV-AQP1 prior to radiation reduces risk of RIX; importantly this would include PSMA Radioligand therapy
- Each year, >50,000 patients receive radiation for head & neck cancer in the US and >25,000 receive PSMA radioligand therapy

MEIRAGTx

AAV-AQP1 Long Term Data and Market Review

April 16, 2026

Patient experience and disease burden: How bad is RIX really? Very bad indeed.

Persistent, late, RIX is a severe, untreatable, lifelong condition with devastating consequences for >30% of survivors of head and neck cancer.

- **Extreme persistent dry mouth, inability to swallow or chew, loss of sense of taste**
- **Major diet restrictions, ongoing weight loss, need for invasive tube feeding**
- **Oral health complications and frequent oral infections, sores and persistent pain.**
- **Uncontrolled dental caries, accelerated loss of dentition requiring major reconstruction**
- **Impaired speech, difficulty sleeping, inability to exercise as faster breathing may lead to choking**
- **Social isolation and refusal to interact with others.**

Poor nutrition, lack of sleep, inability to exercise, continual pain, loss of social interaction have a significant, life-changing impact and may lead to frailty and premature death

*"… **People can't have a normal life**. They go around with these sprays to moisturize the mouth … when **they wake up in the morning and try to open their mouth, the skin tears** and they have mouth ulcers…" Medical Oncologist, AMC (IT)*

"It was like I had paper cut my tongue 100 times and then you suck on a lemon." **JANET**

"If I start choking, I can't get the food back out of my mouth which is really terrifying." **CARRIE**

Etiology of Persistent RIX and Population Size

Persistent RIX is the most frequent and severe consequence of curative radiation treatment for head & neck cancer

- Almost all patients treated with radiation for H&N cancer experience acute xerostomia at the time of radiation
- In 60%-70% of patients, acute radiation induced xerostomia resolves or becomes manageable by 12 to 18 months after radiation
- However, in **~ 30%-40% of patients xerostomia does not resolve** even 2 years after radiation
- **85%** of these patients do not respond to any available therapy
- **Persistent RIX is a lifelong condition that only gets worse with time, with no effective therapies**

Persistent RIX following treatment for H&N cancer is a large population and a completely unmet need:

- In the US: there are **165k prevalent patients** and >20k incidents per year
- Globally (US, EU, Japan) there are **435k prevalent patients** and 48k incidents per year
- A large, commercial opportunity of up to **$3.8bl annual sales** globally and ~ $2bl in US

Mechanism of Action of AAV-AQP1 for treatment of Late Radiation-induced Xerostomia (RIX)

- Salivary glands are particularly vulnerable to radiation
- Damage to salivary glands during radiation leads to acute xerostomia in almost all patients
- Over 12-18 months, damaged glands may remodel, saliva flow restored and xerostomia alleviated or becomes manageable (60%-70%).
- **In 30-40% of patients the damage to salivary glands is irreversible**, the glands fail to recover and xerostomia persists for life.
- AAV-hAQP1 is instilled into the duct of damaged glands and transduces the remaining gland epithelium with the gene encoding the Aquaporin 1 (AQP1), a non-polarized water channel.
- **Expression of the AQP1 makes the epithelium permeable to water and allows water to flow down the concentration gradient into the salivary duct and into the mouth**

AAV-AQP1 Delivery Procedure:

- Small dose delivered locally directly to salivary gland
- Simple in-office procedure
- No general anesthesia or pain
- One-time therapy
- Low cost of goods

Phase1 (n=24): Transformative Clinical Improvements in Xerostomia PRO (XQ) as well as Objective Saliva Flow (UWSFR) Endpoints

Xerostomia Clinical Definition:

- Xerostomia is a purely patient reported condition
- The level of xerostomia symptoms is not correlated to the absolute amount of saliva produced by an individual (ASCO Guidelines)
- However, xerostomia is the result of too little saliva available to wet the mouth and retain normal oral health and function.

Xerostomia Endpoints:

- Xerostomia Questionnaire (XQ) is the standard patient-reported measure of xerostomia
- Unstimulated Whole Saliva Flow Rate (UWSFR) is an objective measure of the change in salivary function

Phase 1 Clinical Data:

- **Compelling 12 month data:**
  - **XQ score** 12-month data demonstrate **"unprecedented" and "transformative"** improvements in xerostomia
  - **USWFR** also showed large increases in water flow into the mouth – the objective measure of AAV-AQP1 MOA
- **Durability of effect :** Phase 1 study shows these **transformative improvements in XQ and UWSFR are maintained out to 3 years**

AAV-AQP1 has the potential to be a disease modifying therapy with durable, transformative benefits for this otherwise severe, lifelong, untreatable condition

Granted Breakthrough Therapy designation in addition to RMAT and ODD

MEIRAGTx

MEIRAGTx

Phase 1 AQUAx Clinical study of AAV-AQP1 for treatment of radiation induced xerostomia

AQUAx: Phase 1 Clinical Study Design

- **Open-label, multi-center, dose-escalation study (4 sites, US/Canada)**
- **One-time administration of AAV-AQP1 to one (unilateral) or both (bilateral) parotid glands**
- **Four dose-escalating cohorts with 3 participants per cohort (n=12 for unilaterally treated and n=12 for bilaterally treated)**
- **All participants are followed for 1-year post-treatment and then invited to enroll in a long-term follow-up study for a total of 5 years**

Primary endpoint

- Safety

Secondary endpoint

- Patient reported measures of xerostomia symptoms
  - Xerostomia Questionnaire (XQ)
  - MD Anderson Symptom Inventory – Head and Neck
  - Global Rate of Change Questionnaire (GRCQ)
- Unstimulated whole saliva flow rate

Cohort	Dose
Unilateral treatment	
1	1×10^{11} vg/gland
2	3×10^{11} vg/gland
3	1×10^{12} vg/gland
4	3×10^{12} vg/gland
Bilateral treatment	
1b	3×10^{10} vg/gland
2b	1×10^{11} vg/gland
3b	3×10^{11} vg/gland
4b	1×10^{12} vg/gland

SAFETY: Primary Endpoint of Phase 1 Study

- AAV2-hAQP1 was generally safe and well-tolerated at all doses tested
- No treatment-related serious adverse events
- No dose-limiting toxicities
- No participant discontinued from the study
- 6 mild, treatment-emergent treatment-related adverse events (TEAEs). All resolved without sequelae.

AQUAx: Xerostomia Questionnaire (XQ) 12 month change from baseline

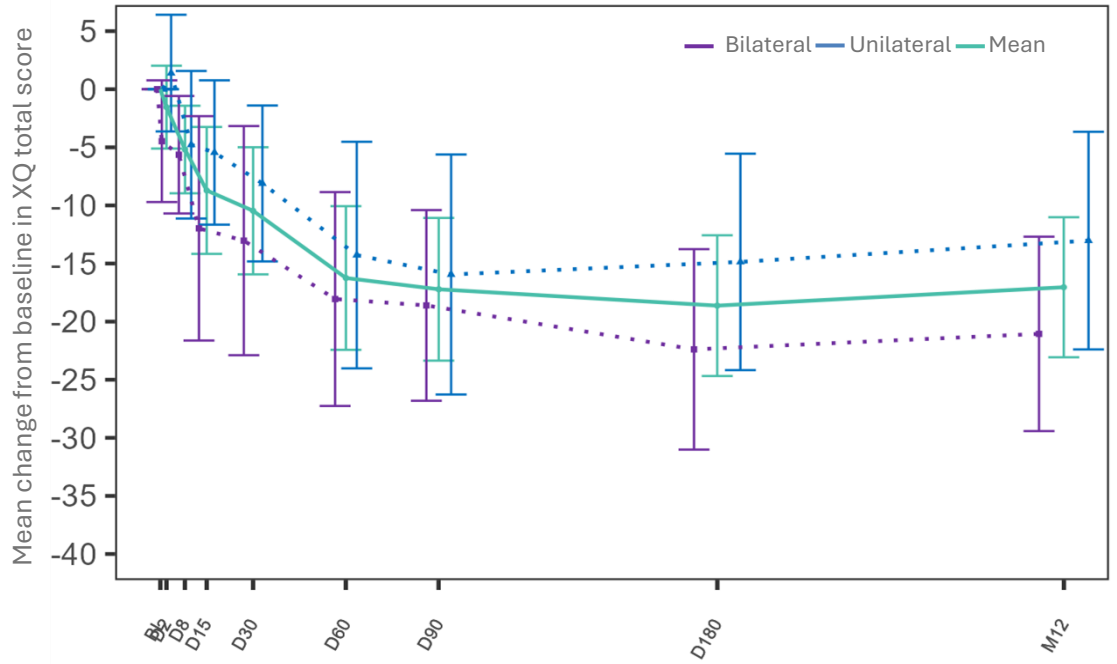
- 8 symptom-specific xerostomia PRO answered by patients with a total **maximum score of 80 points** (higher is worse)
- An improvement (decrease) of **≥8 points** is considered clinically meaningful
- An improvement of **≥10 points** is considered transformative

Transformative improvement: Average XQ score improved by **17 points** (39.5%) at Month 12

Bilaterally-treated participants reported greater improvement than those treated unilaterally, 21 points vs 13 points, with **75% of bilaterally-treated patients reporting transformative (≥10 point) improvement at Month12**

Responses were durable up to 3 years (latest visit)

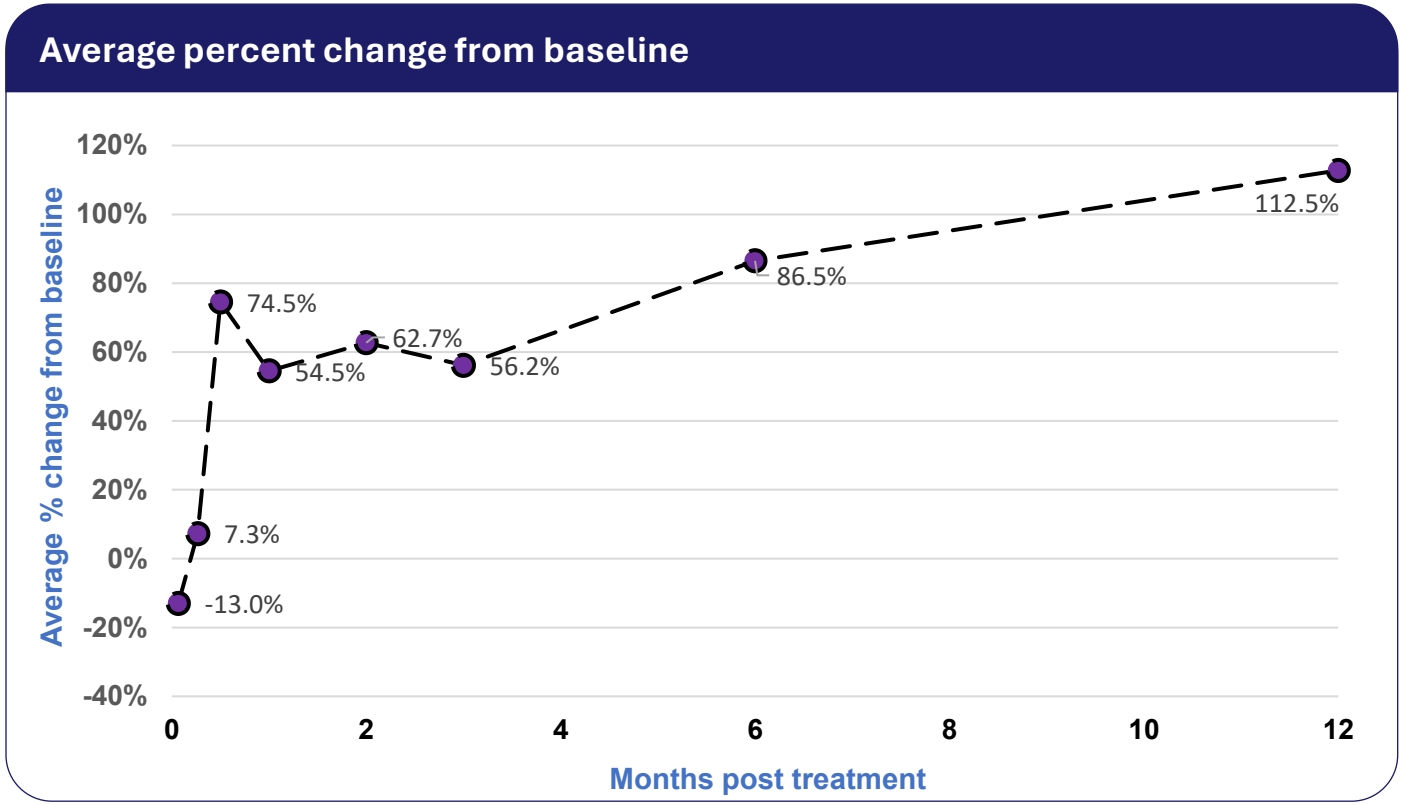
Average change in XQ score



1. Eisbruch A et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001 Jul 1;50(3):695-704. 2. Jabbari S et al. Matched Case–Control Study of Quality of Life and Xerostomia after Intensity-Modulated Radiotherapy or Standard Radiotherapy for Head-and-Neck Cancer: Initial Report. Int. J. Radiat. Oncol. Biol. Phys. 2005;63:725–731.

AQUAx: Unstimulated whole saliva flow rate average percent change from baseline at 12 months pooled unilateral and bilateral cohorts

At Month 12, the Unstimulated Whole Saliva Flow Rate increased by 112.5% from baseline

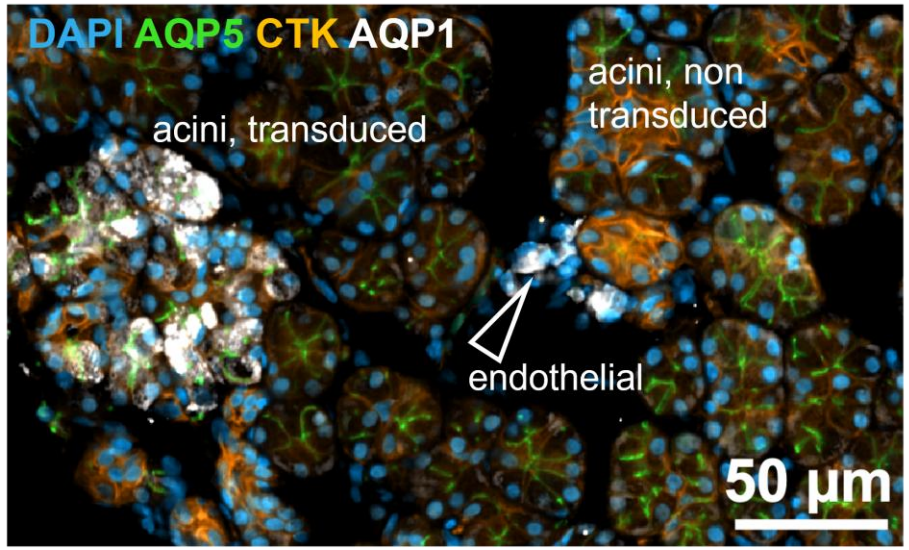


Biopsies indicate that AAV2-hAQP1 persists in the salivary gland

- Core needle biopsies were obtained in 7 participants who enrolled in a NIH Phase 1 study of AAV2-hAQP1 (MGT001).
- **6/7 biopsies showed AAV2-hAQP1 genomes 12-30 months post-treatment**
- There was a trend of increasing copy number of vector genomes with increasing viral vector dose

Participant	Cohort	Dose per gland	Visit of Biopsy	Copy #/ng DNA	Copy #/Cell
AAV001	1	1E10	18 Months	160	0.96
AAV005	1	1E10	24 Months	122	0.73
AAV002	2	3E10	18 Months	236	1.4
AAV019	3	1E11	24 Months	5393	32
AAV020	4	3E11	30 Months	ND	ND
AAV021	4	3E11	12 Months	87390	524
AAV031	5	6E11	12 Months	7313	43

- The image on the right shows a core needle biopsy from a participant in the NIH Phase 1 study
- **AQP1 protein expression was observed in parotid gland cells at 24 months post-treatment**
- Acinar cells in this section express AQP1 (shown in white), whereas they normally express only AQP5 – here shown in green
- Levels of AQP1 protein in transduced acinar cells appear similar to the endogenous levels seen in non-parotid endothelial cells



MEIRAGTx

AAV-AQP1: for treatment of xerostomia

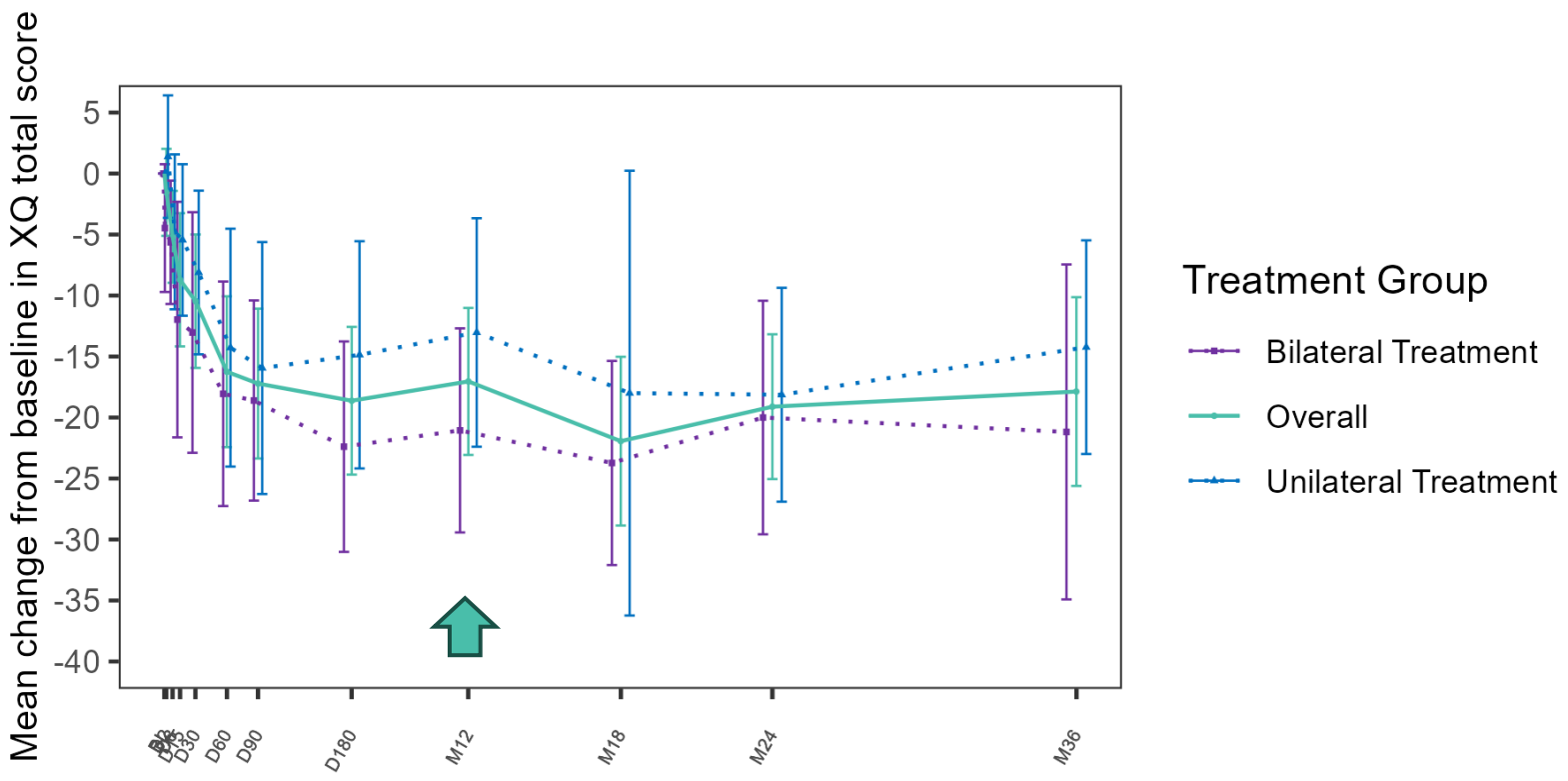
Phase 1 data out to 3 years on all cohorts

Improvements in Xerostomia Questionnaire (XQ) were maintained out to 3 years, demonstrating significant durability of AAV-AQP1

The transformative improvement in the XQ PRO observed in Month 12 were maintained through Month 36

Bilaterally-treated participants reported greater improvement than those treated unilaterally

Average change in XQ score from baseline

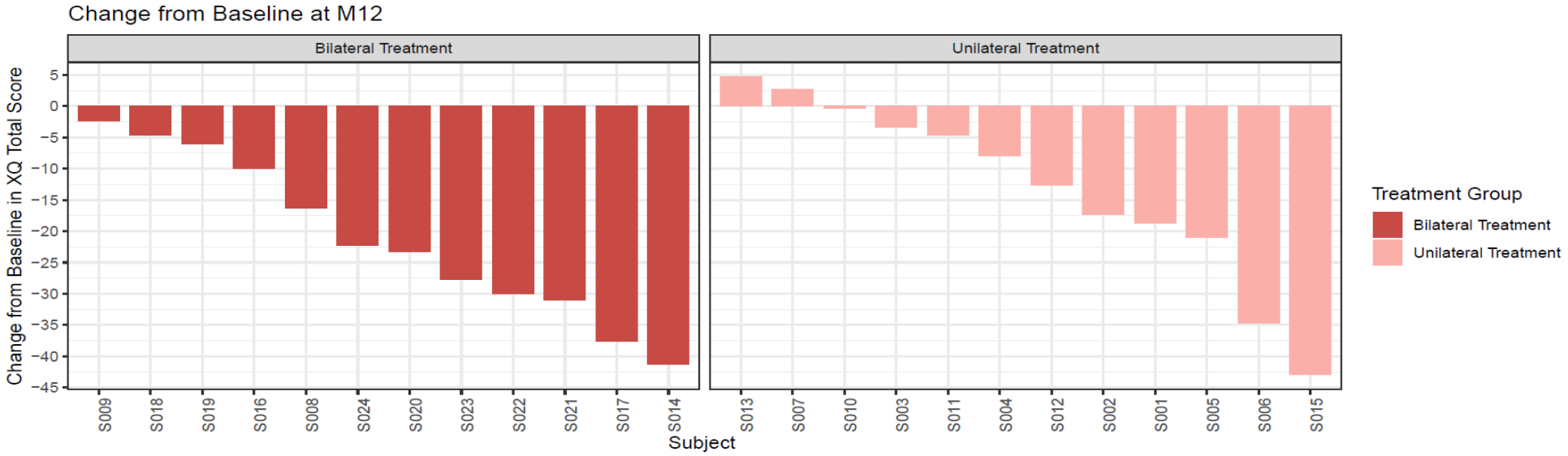


Visit	Baseline	Day 2	Day 8	Day 15	Day 30	Day 60	Day 90	Day 180	Month 12	Month 18	Month 24	Month 36
N_Overall	24	24	23	24	23	23	23	24	24	16	21	21
N_Bilateral	12	12	11	12	11	12	11	12	12	11	11	11
N_Unilateral	12	12	12	12	12	11	12	12	12	5	10	10

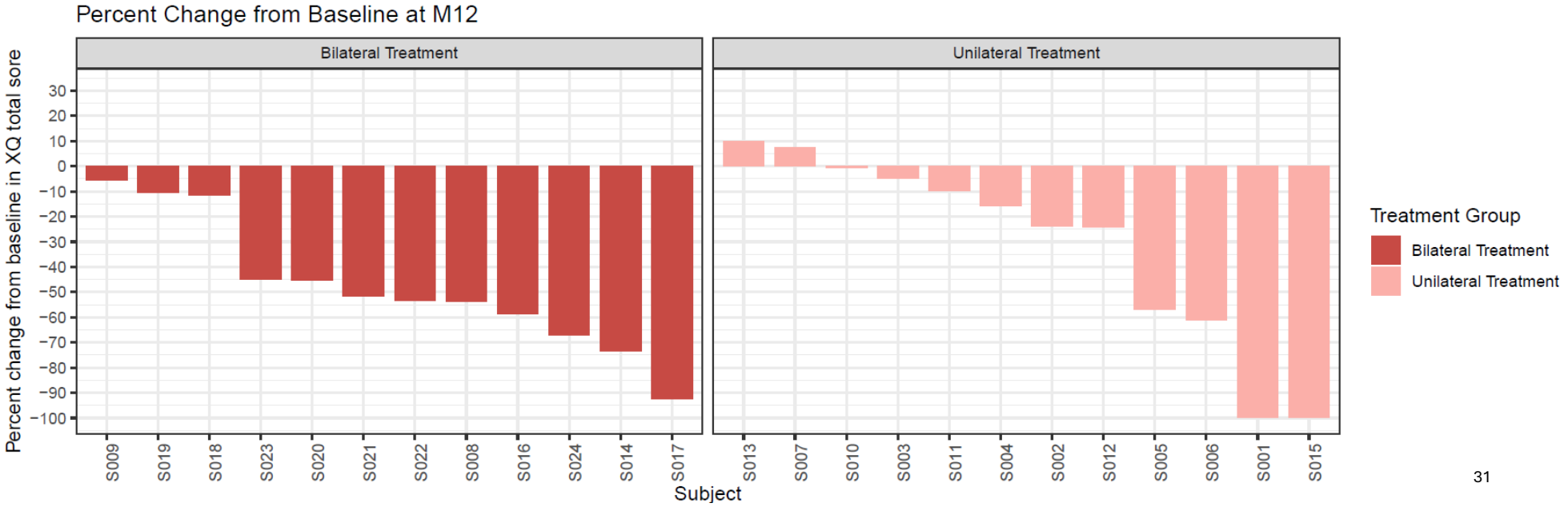
MEIRAGTx

Waterfall Plots of individual subject XQ scores at 12 months: Bilateral and Unilateral: Absolute change and Percentage change

Absolute Change from Baseline



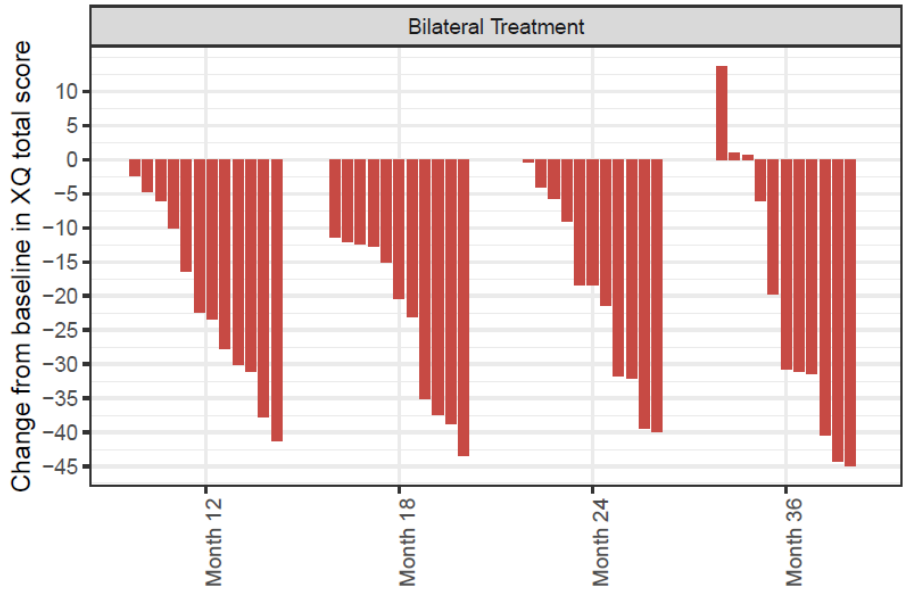
Percent Change from Baseline



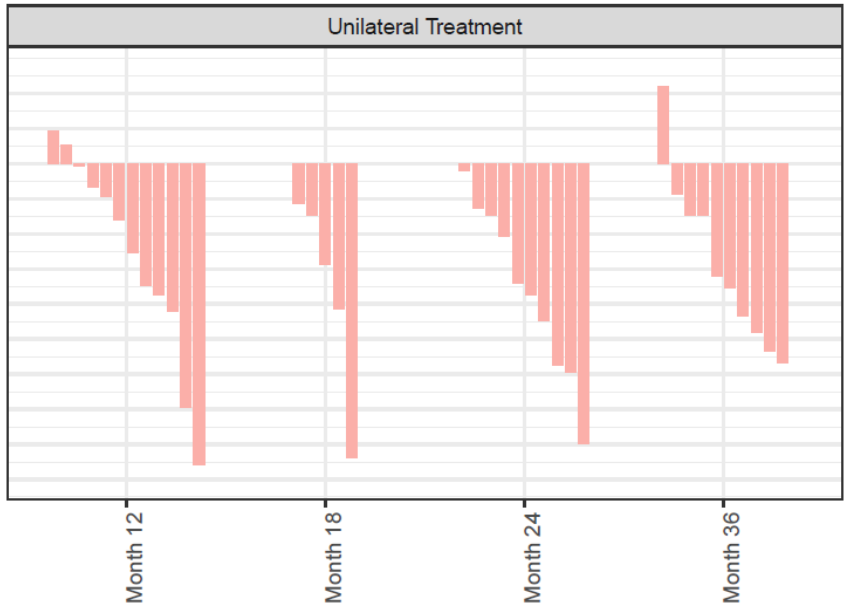
MEIRAGTx

Individual patient data demonstrate durable clinical response over 3 years

Bilateral cohort: Change from baseline (XQ)



Unilateral cohort: Change from baseline (XQ)



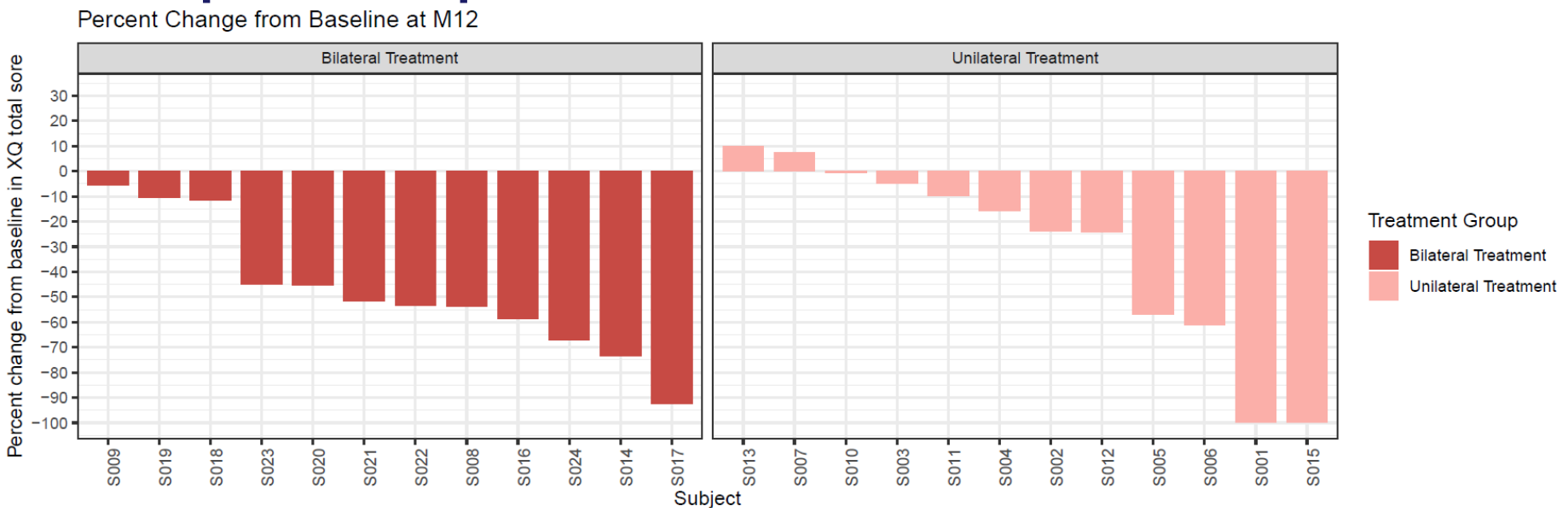
Robust Clinical Response: almost all patients experienced a significant improvement in xerostomia symptoms, with some patients reporting complete **resolution of their xerostomia symptoms**

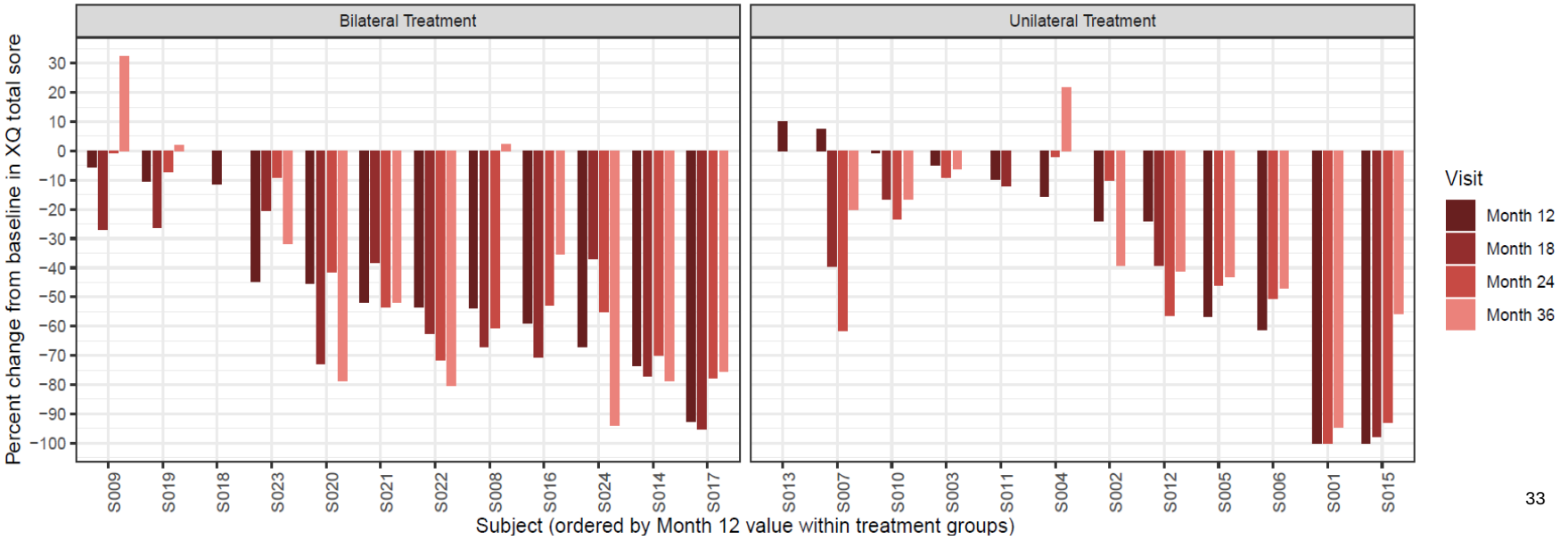
Sustained Long-Term Durability: most subjects maintained or **further improved** their response over the three-year follow-up period

Waterfall Plot of individual subject XQ score at each visit over 36 months showing the consistency of individual patient responses

Individual Patient XQ score at each visit out to 36 months:

- The graphs shows the XQ scores for each patient at 12,18, 24 and 36 months and illustrates the consistency in XQ response for each patient over 3 years.
- Those patients with the the strongest response at 12 months tended to maintain the strongest responses over 36 months, and those with the worst scores at 12 months tended to have the worst scores throughout the study to 36 months.



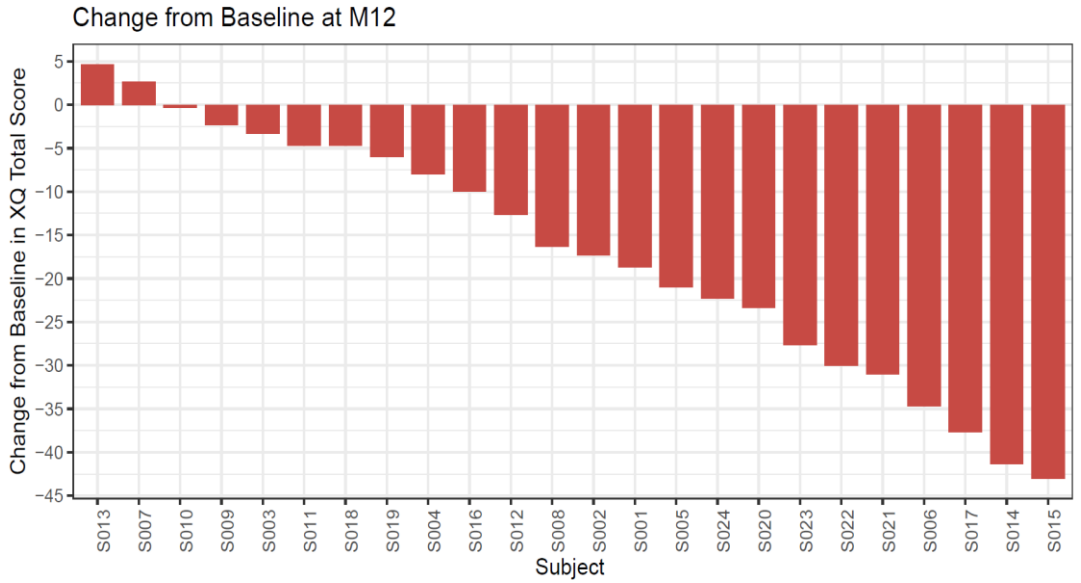


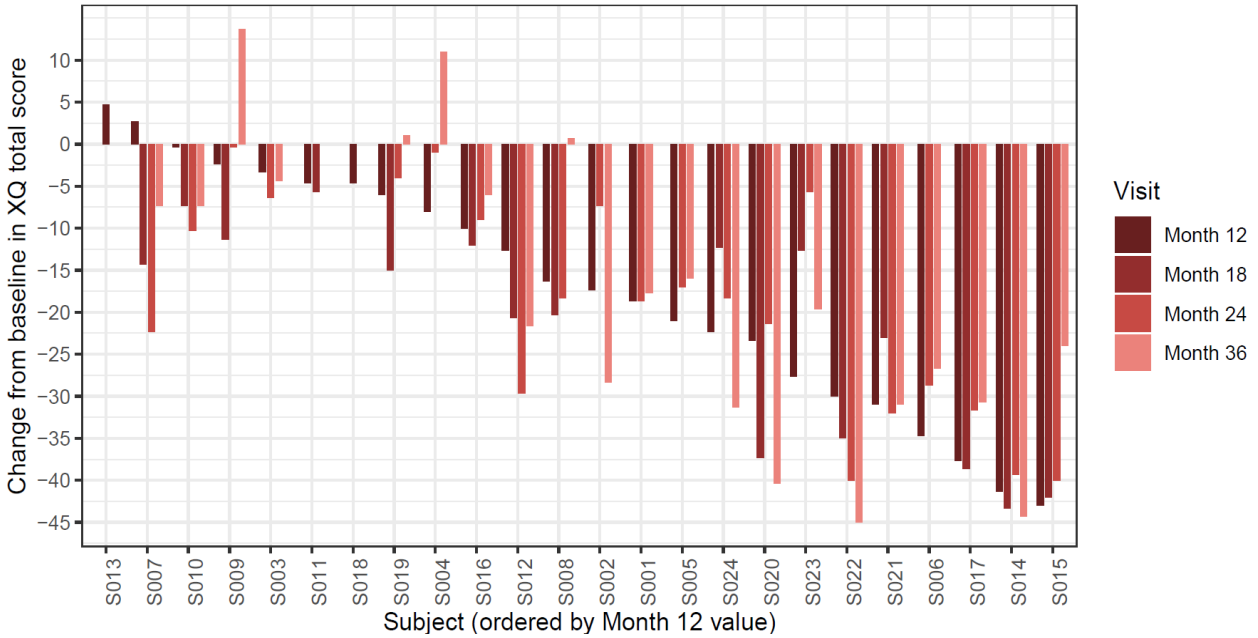
MEIRAGTx

Waterfall Plots of individual subject XQ scores at 12 months: Bilateral and Unilateral Combined

Individual Patient XQ score at each visit out to 36 months: the graphs shows the XQ scores for each patient grouped together at 12,18, 24 and 36 months and illustrates the consistency in XQ response for each patient over 3 years.

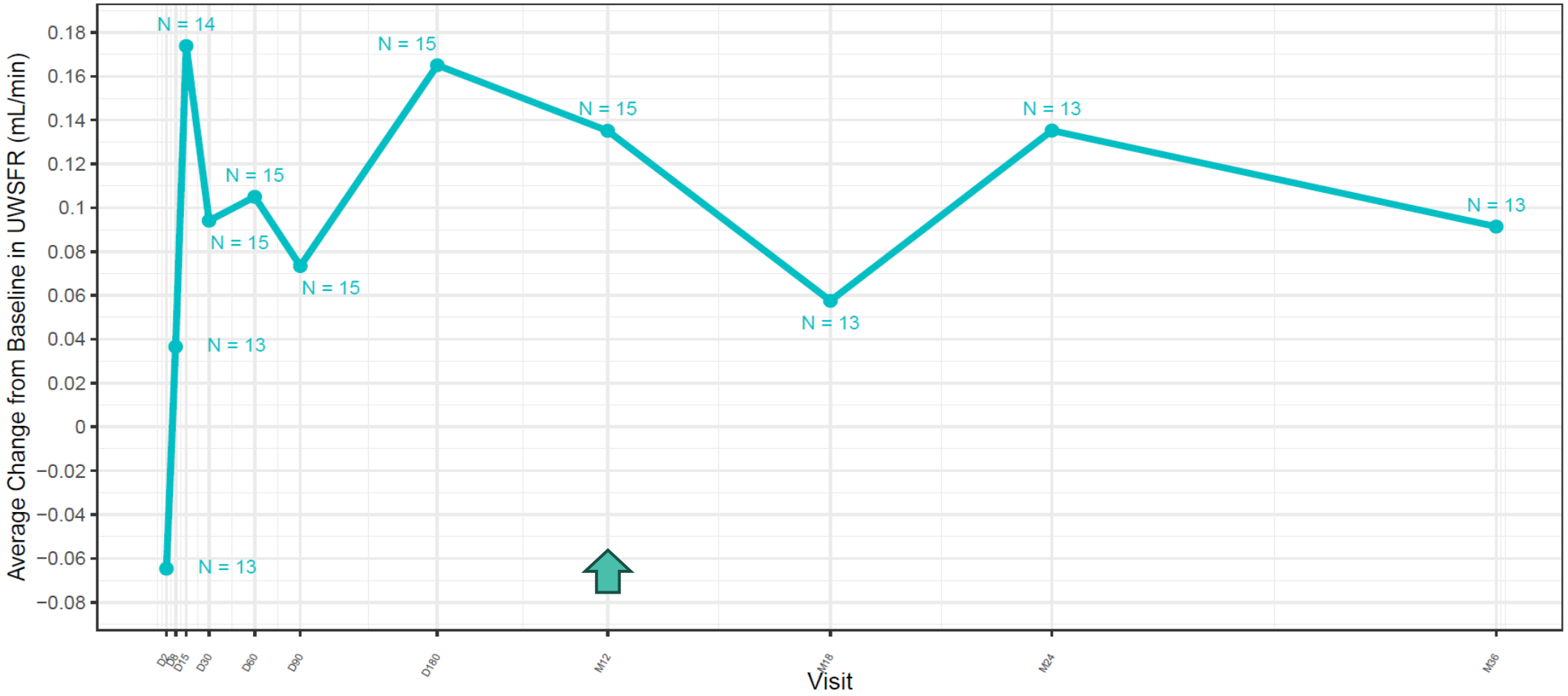
Those patients with the the strongest response at 12 months tended to maintain the strongest responses over 36 months, and those with the worst scores at 12 months tended to have the worst scores throughout the study to 36 months.





MEIRAGTx

Unstimulated Whole Saliva Flow Rate (UWSFR) : Average Change from Baseline out to Month 36 in all treated patients



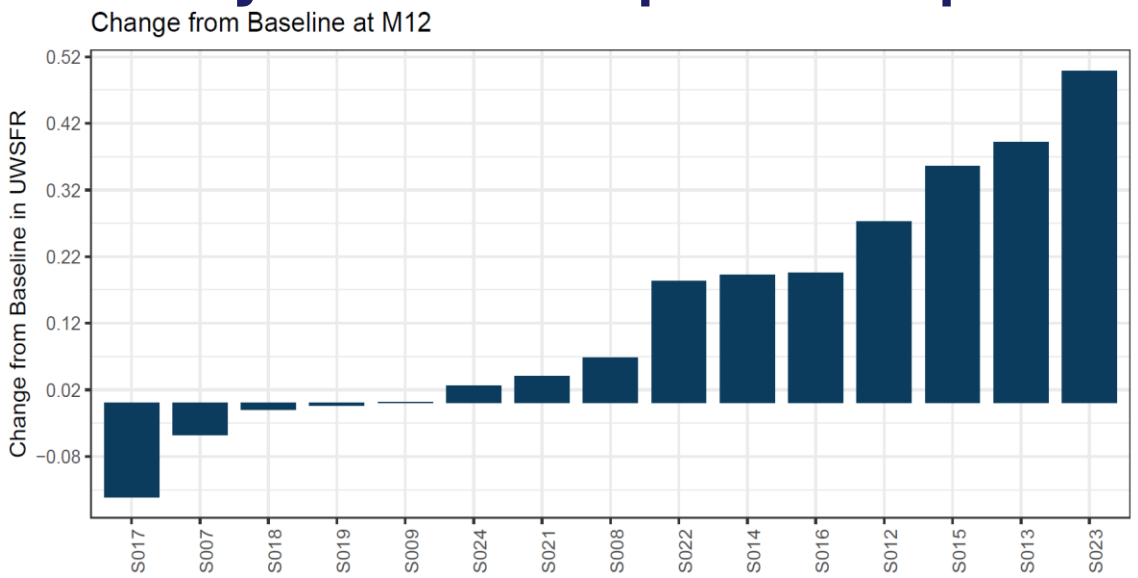
Visit	Baseline	Day 2	Day 8	Day 15	Day 30	Day 60	Day 90	Day 180	Month 12	Month 18	Month 24	Month 36
N_Overall	15	13	13	14	15	15	15	15	15	13	13	13
N_Bilateral	11	11	10	10	11	11	11	11	11	10	10	10
N_Unilateral	4	2	3	4	4	4	4	4	4	3	3	3

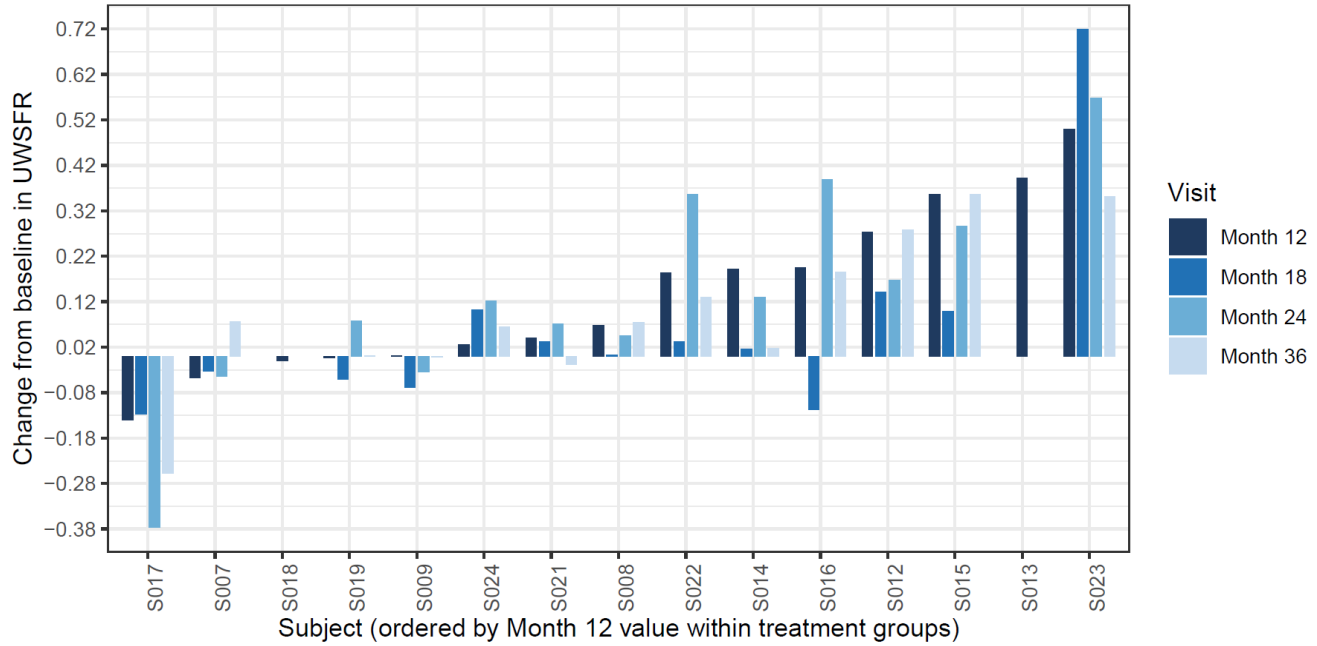
MEIRAGTx

Waterfall Plot of each individual subject UWSFR at each visit out to 36 months with subjects showing the overall consistency of individual patient responses

- **Individual Patient UWSFR score at each visit out to 36 months:** the graphs shows the UWSFR for each patient r at 12,18, 24 and 36 months and illustrates the consistency in response for each patient over 3 years.

- Those patients with the the strongest response at 12 months tended to maintain the strongest responses over 36 months, and those with the worst response at 12 months tended to have the worst response throughout the study to 36 months.

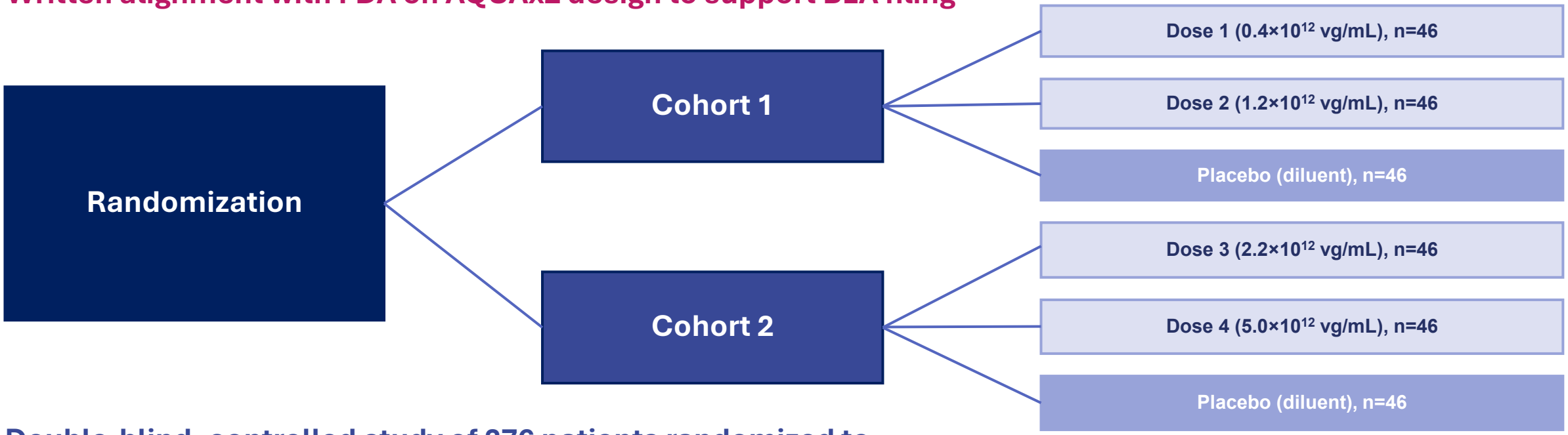




MEIRAGTx

Pivotal MGT-AQP1-201 Study (AQUAx2)

Written alignment with FDA on AQUAx2 design to support BLA filing



Double-blind, controlled study of 276 patients randomized to one of 4 active doses or placebo

- Primary Endpoint - Change from Baseline to Month 12 in modified Xerostomia-specific Questionnaire Total Score
- Key Secondary Endpoint - Change from Baseline to Month 12 in unstimulated whole saliva flow rate (mL/min)
- Other Secondary Endpoints
  - Change from Baseline to Month 12 in Average Dry Mouth Index
  - The Global Rating of Change Questionnaire Score at Month 12
  - Number of participants with treatment-emergent adverse events and serious adverse events

MEIRAGTx

Study Investigator Discussion of Disease Burden, Patient Experience, and Treatment Administration

David Owens, MBCHB, FRCS, MPHIL, PGDME, FFST(Ed)

Consultant Otolaryngologist,
University Hospital of Wales, Cardiff, UK.

David Owens: Impact of Radiation-induced Xerostomia and Limitations of Current Therapies

Severe Clinical Consequences

Grade 2/3 radiation-induced xerostomia causes constant dryness, pain, sores, swallowing difficulties, and altered taste.

- Lifelong condition with profound impact on both patient and caregiver
- Severely affects eating, swallowing, speaking, taste, sleep, and social interaction

Negative Health Effects

This condition can cause weight loss & frailty, malnutrition, communication difficulties, and emotional distress

Dental Complications

Loss of saliva's antimicrobial protection accelerates dental decay, complicating patient management

Limitations of Current Therapies

- Gels and washes provide minimal, short-lived symptomatic relief
- Currently, there are no effective disease-modifying therapies

Clinical Experience, Feasibility, and Implications for Practice

Clinical Trial Outcomes

AQUAx Phase 1 trial showed promising efficacy, safety, and long-term durable benefits for patients.

Clinical Integration

Procedure fits existing clinical skills, requires minimal training, standard outpatient equipment, and is quick.

- Procedure aligns with existing skills of: ENT Surgeons, Oral medicine specialists and oral and maxillofacial surgeons
- No operating theatre or complex infrastructure procedure performed in a standard outpatient clinic chair
- Bilateral treatment in <1hr enabling routine clinic integration
- Multiple procedures a day possible

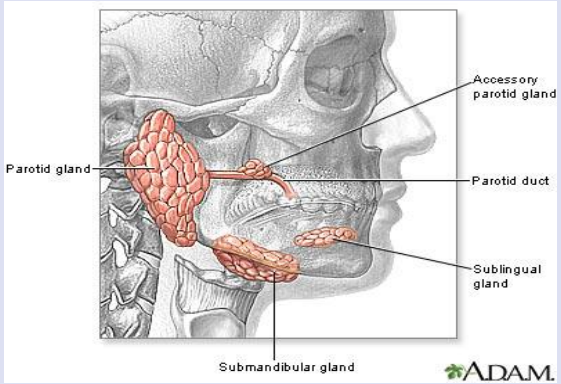
Potential to change standard of care

AAV-hAQP1 therapy could become the standard care for moderate-severe xerostomia in head and neck cancer survivors.

- One-time treatment with high tolerability
- Durable clinical benefit and ease of administration

Minimally Invasive Procedure

Retrograde intraductal delivery of AAV-hAQP1 is straightforward, tolerable, and typically pain-free for patients.



MEIRAGTx

Study Investigator discussion of disease burden, patient experience, and treatment administration

Michael Brennan, DDS, MHS

Professor and Chair, Department of Oral Medicine/Oral & Maxillofacial Surgery, Wake Forest University School of Medicine

Atrium Health Carolinas Medical Center, Charlotte, NC

Dr. Brennan: Transformative, Disease-Modifying Potential for A Serious, Lifelong Debilitating Disorder

Debilitating Side Effect of Radiotherapy

Radiation-induced xerostomia occurs in virtually all patients receiving radiation treatment for head and neck cancer

- In 30-40% of patients, xerostomia persists as a lifelong condition
- Severely affects eating, swallowing, speaking, taste, sleep, and social interaction

Meaningful Decline in Overall Health and Well-being

- Patients suffer from oral infections, uncontrolled dental caries, pain & mouth sores, and difficulty speaking
- Difficulty eating and swallowing result in nutritional challenges and the potential need for a feeding tube
- Choking because of faster breathing can limit exercise
- Social Isolation

Lifelong Burdensome Consequence of Successful Treatment for Cancer

- Despite prevalence and significant impact on patients lives, there is no effective treatment

One-Time Gene Therapy Targeting the Root Cause of the Disorder

AAV-hAQP1 designed to restore activity within salivary tissue

- Re-establishes function at a biological level
- Meaningful shift in therapeutic intent

Meaningful Improvement

- Dramatic, consistent, and clinically meaningful improvements in daily functioning
- Patients are able to eat, speak, exercise, and re-engage socially

Transformative Observed Benefits

- Durable responses last > 3 years after treatment with AAV-hAQP1
- Persistence of the transformative benefits from changes to the underlying biology of the condition
- Benefits are transformative, durable and potentially disease modifying

MEIRAGTx

Global Survey of Physicians and Payors with 3 year durability data

Commercial Opportunity

Clinicians view the strong response rates, curative treatment, and durability of effect as highly meaningful in this unmet need

Clinician Preference Share: ~78% global adoption based on clinician preference

Clinician-stated preference share weighted by patient volume — **~78%**

*Overstatement-adjusted preference share**** — **~52%**

Physicians highlight:

- **Transformative benefit in meaningful endpoints:** Both PRO and water flow impact unprecedented
- **Minimally invasive onetime** dosing fits easily into clinical practice
- **Strong 3-year durability** seen as evidence of possibly permanent response
- **Good safety profile**
- Viewed as **a simple, one-time treatment leading to a disease modifying effect on a severe, otherwise untreatable lifelong condition.**

*"… **I will say if the data shows that it is providing durable responses, maybe I will try to do it for all [Grade 2 or Grade 3 (moderate or severe)] patients** …"* Medical Oncologist (U.S.)

*"… **In the course of my career, I have had four or five experiences where I saw something and I said, 'That is freaking awesome'. This is something that I have to integrate into my practice, and this is one of them …"*** Oral and Maxillofacial Surgeon, (U.S.)

*"… **This is the first disease-modifying treatment for xerostomia, and I am very excited that it might be available**…"* Medical Oncologist (U.S.)

"Patients will be motivated to get that product, otherwise the status quo is that the xerostomia they get from radiation will be permanent. That would be a big motivator for patients to get this one-time procedure" Radiation oncologist (US)

"A strength is, of course, the way of application. It's relatively easy in the outpatient setting without severe surgery and anesthesia" Medical oncologist (DE)

MEIRAGTx

Source: Based on survey and interview feedback with U.S., UK+EU4, JP physicians (N=75); * Overstatement adjustments were applied to individual responses as follows – 80% for "Definitely would", 60% for "Probably would", 25% for "Might or might not", and 0% for "Probably would not" and "Definitely would not"

Late moderate to severe RIX: A completely unmet need and large potential market

Peak global revenue is estimated to be ~$3.7B, with a steady state of ~$3.2B

Clinician perspectives	• **Strong responses in meaningful measures:** PRO and salivary flow, **long-lasting benefit** following a **simple one-time treatment** • HCPs view AAV-AQP1 as a **highly differentiated, disease-modifying treatment** • **Physician-stated preference share** is **~78%** and leading to **~ 52%** usage with overstatement adjustment
Epidemiology and disease landscape	• **Persistent RIX** three or more years post radiation treatment is **severe, lifelong disorder** with no effective treatment • **Prevalence:** 165k US only ; 435k Global • **Annual Incidence:** ~20K US only ; ~ 48k Global
Payer perspectives	• U.S. list price of **~$150K** and **15-20% GTN** • Market access coverage is estimated at **~90%**
Projected RIX revenue	• **Global potential net revenue**: **peak at ~$3.7B** reaching a **steady state of ~$3.2B** in the late 2030s • **U.S. net revenue**: **peak at ~$2.0B** reaching a **steady state of ~$1.8B** in the late 2030s • **Cumulative treated globally:** 250K/730k, **32%-37%** over 10 years

MEIRAGTx

Source: Primary market research commissioned by MeiraGTx

Access to >60% of the U.S. population >55 years old with HNC by targeting a concentrated set of 15 major metro areas with a 3-hour driving catchment radius

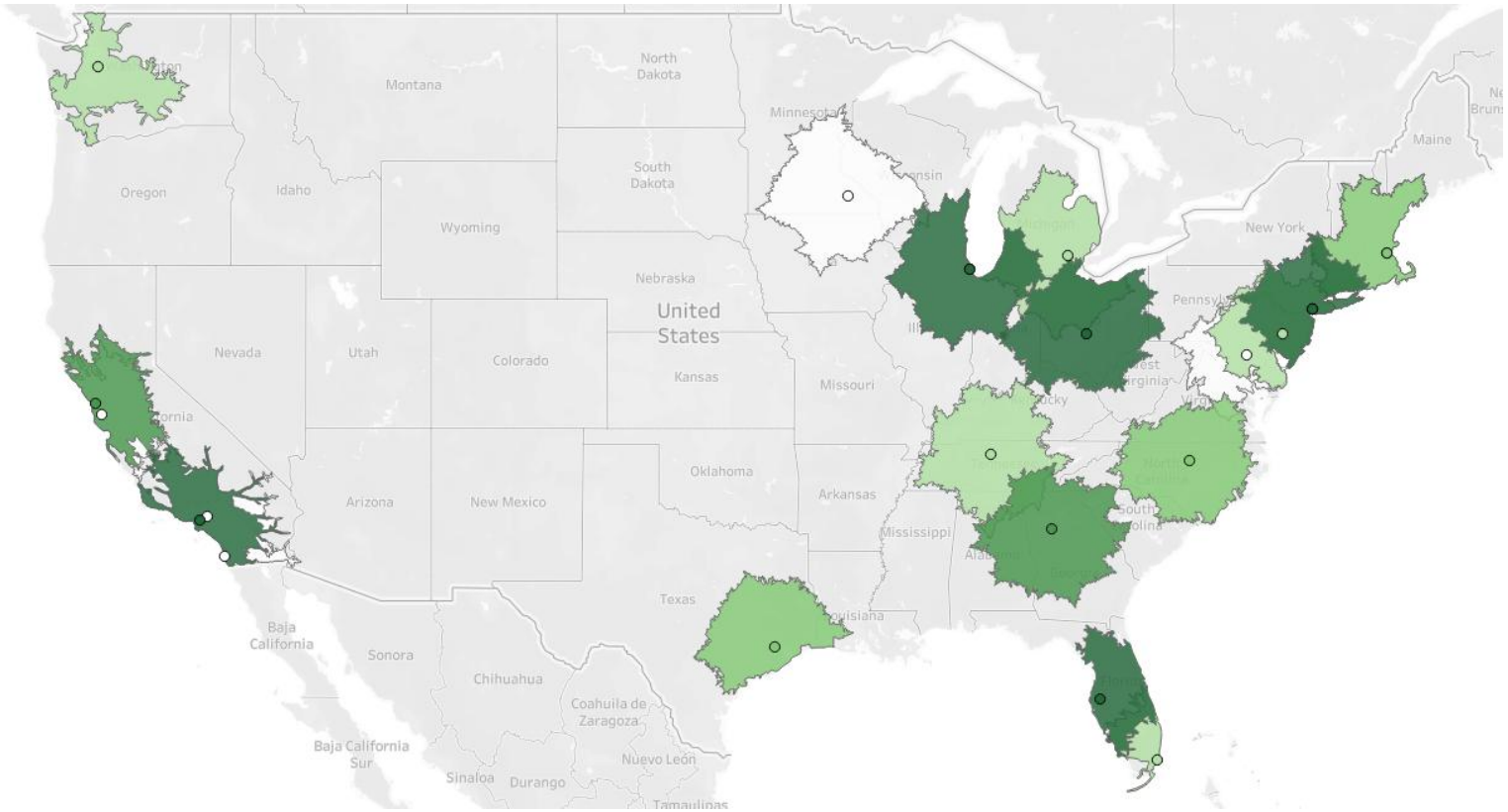
U.S. Population and HNC hospitals

Key assumptions and inputs

- HNC is **distributed evenly** across the U.S. population
- Population **>55 years** considered*
- Catchment areas include a **drive radius of 3 hours; NYC was prioritized over others in radius** due to hospital strength
- **Top 25 HNC hospitals** were identified using overall **cancer ranking (e.g., U.S. News), ENT specialty ranking, surgical volume, clinical trial leadership, and NIH research funding**

Key conclusions

Access to >60% of the population would require **15 sites**



Optimized number of sites that account for ~X% of the population: 30% | 40% | 50% | 60% | >60%

MEIRAGTx

Note: *>80% of HNC is in population >55 years old
Source: U.S. Census; Hospital websites

Of the leading head and neck cancer centers, MeiraGTx can optimize reach based on the cumulative population addressed; diminishing incremental reach is seen after ~17 hospitals in the top 25

Optimized number of sites that account for ~X% of the population: 30% | 40% | 50% | 60% | >60%

	Metro area	Key HNC Hospital	Catchment population (% of total pop.)	Cumulative population (% of total pop.)
1	New York, NY	Memorial Sloan Kettering Cancer Center	10.8%	10.8%
2	Los Angeles, CA	UCLA Jonsson Comprehensive Cancer Center	6.3%	17.1%
3	Chicago, IL	Northwestern Medicine / Robert H. Lurie Cancer Center	5.4%	22.4%
4	Columbus, OH	Ohio State University / James Cancer Hospital	5.0%	27.4%
5	Tampa, FL	Moffitt Cancer Center	4.6%	31.9%
6	Atlanta, GA	Winship Cancer Institute / Emory University	4.0%	35.9%
7	San Francisco, CA	UCSF Helen Diller Family Comprehensive Cancer Center	3.9%	39.8%
8	Boston, MA	Massachusetts General Hospital	4.7%	43.2%
9	Durham, NC	Duke Cancer Institute	3.7%	46.6%
10	Houston, TX	MD Anderson Cancer Center	3.1%	49.7%
11	Philadelphia, PA	University of Pennsylvania / Abramson Cancer Center	11.9%	52.6%
12	Nashville, TN	Vanderbilt-Ingram Cancer Center	2.8%	55.1%
13	Ann Arbor, MI	University of Michigan Rogel Cancer Center	4.8%	57.5%
14	Miami, FL	Sylvester Comprehensive Cancer Center / Univ. of Miami	3.1%	59.5%
15	Seattle, WA	University of Washington / Fred Hutchinson Cancer Ctr	2.0%	61.5%
16	Rochester, MN	Mayo Clinic Cancer Center	1.9%	63.3%
17	Baltimore, MD	Johns Hopkins / Sidney Kimmel Comprehensive Cancer Ctr	7.5%	64.5%
18	Stanford, CA	Stanford Cancer Institute	3.8%	64.5%
19	San Diego, CA	UC San Diego Moores Cancer Center	5.9%	64.6%
20	Duarte, CA	City of Hope Comprehensive Cancer Center	6.3%	64.6%

Note: *>80% of HNC is in population >55 years old; Remaining hospitals in the top 25 are NewYork-Presbyterian / Weill Cornell & Columbia (10.8%), Mount Sinai Hospital – Head and Neck Institute (10.8%), Dana-Farber / Brigham and Women's Cancer Center (4.7%), NYU Langone Perlmutter Cancer Center (10.8%), University of Chicago Medicine (5.4%), however, because catchment areas have significant overlap, they do not add significant population to the cumulative number of patients reached

Source: U.S. Census; Hospital websites

MEIRAGTx

AAV-AQP1: Program highlights

AAV-AQP1 has the potential to become the standard of care for patients with late, grade 2/3 radiation-induced xerostomia based on its disease-modifying mechanism and meaningful improvements in both objective and subjective outcome measures

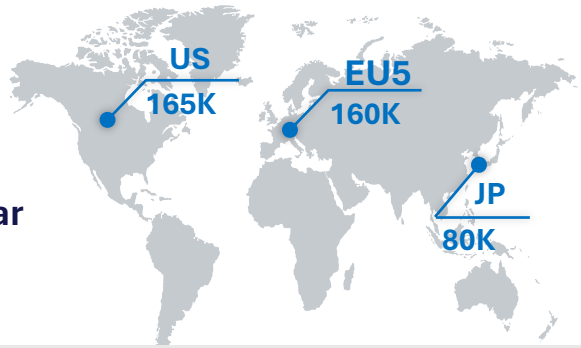
- Severe condition with no effective treatment
- Disease-modifying therapy
- One-time, local delivery
- Outpatient setting
- Favorable safety profile
- Durable efficacy

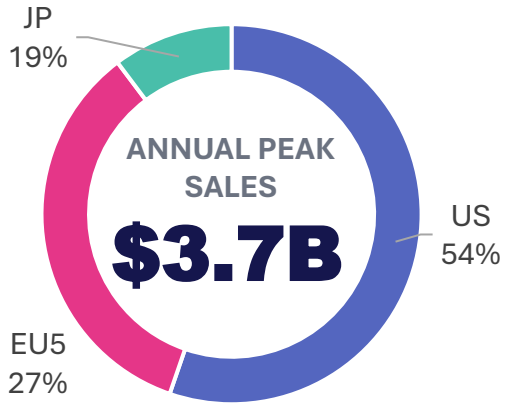
- One-time, minimally-invasive, local delivery of a single, small dose delivered through an outpatient cannulation procedure with which ENTs and dentists trained in oral medicine are familiar with
- Unprecedented improvement in **PRO (XQ) and Objective endpoints (UWSFR)** in Phase 1 treated patients
- Expected to provide **durable long-term benefit** in severely affected patients with no other effective current treatment options
- AAV-AQP1 treatment for grade 2/3 xerostomia is a large commercial opportunity, very concentrated
- AAV-AQP1 uses a small dose with low associated COGS
- Granted Orphan Drug, RMAT and Breakthrough Therapy designations by FDA
- Written alignment with FDA on clinical and CMC and requirements of BLA supportive Phase 2 study
- Pivotal Phase 2 study data and BLA filing expected in Q2 2027, targeting early 2028 launch in the US
- **Data from the long-term follow up study for all cohorts shows durable and consistent intra-patient responses in both PROs and saliva production out to 36 months**

Significant commercial opportunity for a first-in-class treatment for large population of persistent RIX with severely debilitating unmet need

435K SIGNIFICANT PATIENT POPULATION

435k patients currently living with persistent grade 2/3 late RIX in the 7 major markets, with **48K new cases diagnosed each year**





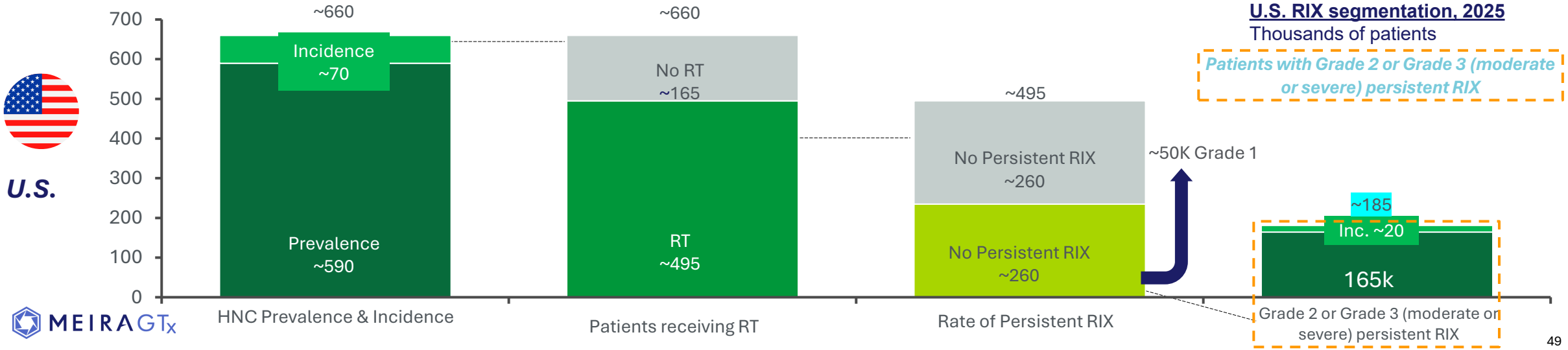
Annual peak sales (**late RIX only**) of **$3.7 billion globally**

Opportunities for label expansion and increased revenues:

- PSMA radioligand therapy
- Sjogren's disease

U.S. net revenue: peak at ~$2.0B reaching a **steady state of ~$1.8B** in the late 2030s

Prevalence: 165k in the US; **Annual Incidence:** ~20K



MEIRAGTx

MEIRAGTx

Bota-vec for the treatment of X-Linked Retinitis Pigmentosa (XLRP)

- Phase 3 complete (n=95)
- Phase 3 conducted at 32 of the leading global sites for Inherited Retinal Disease (IRD) in North America and Europe
- Granted PRIME and Fast Track designations, and US and EU Orphan Drug Designations
- BLA and MAA filing preparation under way

Bota-vec Opportunity Overview: High-Value, De-Risked Program with Potential Near-Term Approval and Launch

Totality of Phase 3 data demonstrates benefit of treatment

- Significant improvements in each of the domains of vision: **functional vision, retinal function and visual function**
- Multiple statistically significant secondary endpoints demonstrate clinically meaningful benefit
- Convergent positive signals across objective (LLVA, perimetry) and subjective (PROs) measures
- Safety profile expected and manageable across both Phase 1 and Phase 3 studies (n= 137) with further improved immune safety demonstrated in the Phase 3 (n=95)

High Unmet Need

- Bota-vec addresses a severe unmet need with no approved disease-modifying therapies
- Demonstrates improvement in each domain of vision in an otherwise inexorably degenerative disease resulting in complete blindness
- Patients report life changing impact of therapy resulting from meaningful improvement in vision.

Commercial Potential

- Significant market >20,000 US and EU
- **~ $1.7 billion* projected peak sales and ~ $7.7 billion** cumulative sales over 10 years**
- Low cost of goods (<$10k per patient) high margin product
- **Strong launch anticipated ~** several hundred patients identified for treatment across a small number of centers of excellence
- 32 of these leading sites participated in the global Phase 3. >60 surgeons trained for optimal delivery.
- And several hundred patients are known to be waiting for treatment

Regulatory Pathways

- Consistent, highly statistically significant, clinically meaningful Phase 3 data across secondary endpoints supports positive approvability dialogue
- **EMA:** MeiraGTx intends to file MAA based on totality of data; EU PRIME and ODD designations
- **FDA:** MeiraGTx intends to return to FDA to discuss the potential route to approval
- Precedent for totality-of-evidence with a trend in primary approvals in rare genetic diseases and previous IRD treatment, EU and US
- Strong support and engagement from patient advocacy groups (FFB, retina UK, FB), physicians, >30 global KOLs, and patients KOLs and patient advocacy groups lobbying for approval across US, EU and Japan

MEIRAGTx

*, ** Revenue projections are from investment bank and demand forecasts using Luxturna pricing, 30% GTN as benchmark

Bota-vec status: awaiting BLA and MAA filings

Largest global development program in a severe Inherited Retinal Disease (IRD) completed with compelling data indicating statistically significant and clinically meaningful benefits across every domain of vision supporting global approval:

- **Phase 3 complete (n= 95)** conducted at 32 of the leading global sites for IRD sites in N. America UK EU and Japan
  - Novel primary endpoint (VMA, Maze) while not achieving statistical significance showed a positive trend with **treated patients 2.4x more likely to respond** than untreated
  - Statistically significant and clinically meaningful **improvements** demonstrated in secondary endpoints in **all domains of vision**
  - **Significant clinically meaningful responder analysis** comparing treated and untreated patients using any endpoints in each of the domains of vision
  - **Significant PRO data** – particularly ability to function in low light, independence, emotional well being, strong concordance of scripted interviews with clinical data
  - **Strong safety profile -** expected and manageable across both Phase 1 and Phase 3 studies **(n= 137)** with further improved immune safety demonstrated in the Phase 3 (n=95)
- **Japan** four Phase 3 patients treated in Japan with 100% response rate, PI reported an extraordinary 40-letter gain in one patient LLVA
- **Phase1/2 study (n=42)** supportive of safety as well as efficacy

Commercial Manufacturing Status:

- **PPQ complete:** MeiraGTx is the commercial manufacturer of bota-vec. PPQ is complete with 3 successful batches of each DS and DP produced; several hundred vials are available for commercial release.
- **Commercial CMC/QC licenses in hand:** MeiraGTx has been granted commercial licenses for both viral vector manufacturing and QC facilities for AAV-RPGR manufacturing as well as QC.

Strong physician and patient advocacy group (FFB) support for approval of bota-vec

Foundation for Fighting Blindness (FFB) Open Letter

In June 2025, the FFB published a public letter signed by 30 leading retinal specialists urging J&J to seek approval for bota-vec based on "life changing improvements after treatment in the Phase 3 LUMEOS trial".

> *"The vision improvements in LUMEOS have been life changing for many patients. Both objective measures and subjective reports demonstrate clear and meaningful efficacy... **The Foundation and trial investigators feel it is incumbent upon J&J to urgently pursue regulatory approval** to make the vision-restoring treatment available to the global XLRP community."*

Reference: FFB Public Letter, June 2025

Patient Voices from LUMEOS Trial Quoted in FFB Letter

> **"The improvement... has been nothing short of remarkable**. ...I would do anything within my power to have the same life-changing opportunity extended to my untreated eye."

> "The treatment has dramatically improved my eyesight. **I used to need a cane at night... and now I no longer need to use a cane."**

> "**I saw stars for the first time** and clouds at night! It was amazing."

> "Tasks that were once frustrating... like moving around safely in dim rooms or walking outdoors after sunset, **have become noticeably easier... restored a sense of independence**."

Bota-vec commercial opportunity:

Launch into concentrated, educated KOL market with commercial supply manufactured in-house at MeiraGTx

Projected cost-effective launch into a concentrated group of educated physicians and patients globally

- Most IRD patients are seen by a **small community of connected KOLs globally**
- We believe a very **large majority, (~ 80%) of RPGR patients globally**, are under the care of such physicians at **~ 40-50 sites US, EU, and Japan**
- This includes the **32 sites who participated in the Bota-vec Phase 3 study,** and all of these global KOLs are known to MeiraGTx through our decade old relationships with the Moorfields Eye Hospital in London and other leading hospitals
- **Over 60 surgeons were trained in bota-vec** delivery for the Phase 3 – there were minimal surgical complications and the safety profile was as expected and improved in the Phase 3 compared to the Phase 1
- KOLs and patient advocates globally are **lobbying for approval** with patients waiting for treatment globally
- **Several hundred patients already identified** in patient registry and at leading hospitals globally
- **Commercial material for release:** PPQ successful with several hundred vials available at MeiraGTx for potential commercial launch
- **MeiraGTx is the commercial manufacturer** with end-to-end **control of drug supply and guaranteed capacity** to support a rapid launch. MeiraGTx holds manufacturing and QC commercial licenses in UK (MHRA) and in Ireland (HPRA)

MEIRAGTx

Phase 3 LUMEOS study of botaretigene sparoparvovec (bota-vec)

Summary of Data

Source: Oral presentation at FFB ARVO 2025 meeting and publication in preparation

Bota-vec Phase 3 Pivotal Study Results

Consistent and Robust Efficacy Across Objective & Subjective Measures
These Endpoints Reflect Significant and Clinically Meaningful Improvement in Every Domain of Vision

Category	Functional Vision		Retinal Function			Visual Function	Safety
Assessment	VMA* (binocular) PRIMARY	PRO: LLQ Extreme lighting domain score	Static perimetry responder (central 30 degrees)	Static perimetry responder (full field)	Retinal sensitivity (central 10 degrees)	Low luminance visual acuity (LLVA, ETDRS letters)	Intraocular inflammation
Results	↑ †	↑ ‡	↑ ‡	↑ ‡	↑ ‡	↑ ‡	Expected, acceptable, and manageable
Treatment difference (±95% CI)	13.4% (-3.6%, 30.5%) *P value = 0.247*	7.29 (2.29, 12.38) *P value = 0.006*	38.1% (21.4%, 54.7%) *P value = 0.001*	36.6% (18.2%, 54.9%) *P value = 0.001*	1.24 dB (0.54, 1.94) *P value = 0.001*	4.75 ETDRS letters (1.64, 7.86) *P value = 0.003*	

*VMA is a novel assessment first used in this study. †Results trending in anticipated direction.‡P<0.05
Full analysis set population (observed data). Includes participants randomized to both doses.
BCVA, best-corrected visual acuity; bota-vec, botaretigene sparoparvovec; ETDRS, Early Treatment Diabetic Retinopathy Study; LLQ, low luminance questionnaire; LLVA, low luminance visual acuity; PRO, patient-reported outcomes; VMA, vision-guided mobility assessment.

Bota-vec Phase 3 Pivotal Study Results: Highly statistically significant and clinically meaningful benefit in multiple secondary endpoints every domain of vision

Primary Endpoint	Pooled treated (n = 55)	Control group (n = 30)	Between-group difference (pooled treated group minus control) (95% CI)	P-value
VMA responders[1] (binocular), %	27.3%	13.3%	13.4% (-3.6%, 30.5%)	0.247†
Secondary Endpoints				
Change in MRS10[4], LS mean (SE)	0.88 (0.22)	-0.36 (0.29)	1.24 (0.54; 1.94)	**0.001**
Pointwise responders in full visual field[2], %	58.2%	23.3%	36.6% (18.2%, 54.9%)	**0.001**
Pointwise responders in the central 30 degrees[2], %	47.3%	10.0%	38.1% (21.4%, 54.7%)	**0.001**
Change in mLLQ Extreme lighting domain score, LS mean (SE)	1.80 (1.50)	-5.49 (2.05)	7.29 (2.20; 12.38)	**0.006**
Change in LLVA[4], LS mean (SE)	6.86 (0.94)	2.11 (1.26)	4.75 (1.64; 7.86)	**0.003**
Change in MRS90[4], LS mean (SE)	-0.00 (0.19)	-0.93 (0.26)	0.92 (0.29; 1.55)	**0.004**

Significant improvements in Patient Reported Outcomes (PRO) questions related to everyday function and quality of life:

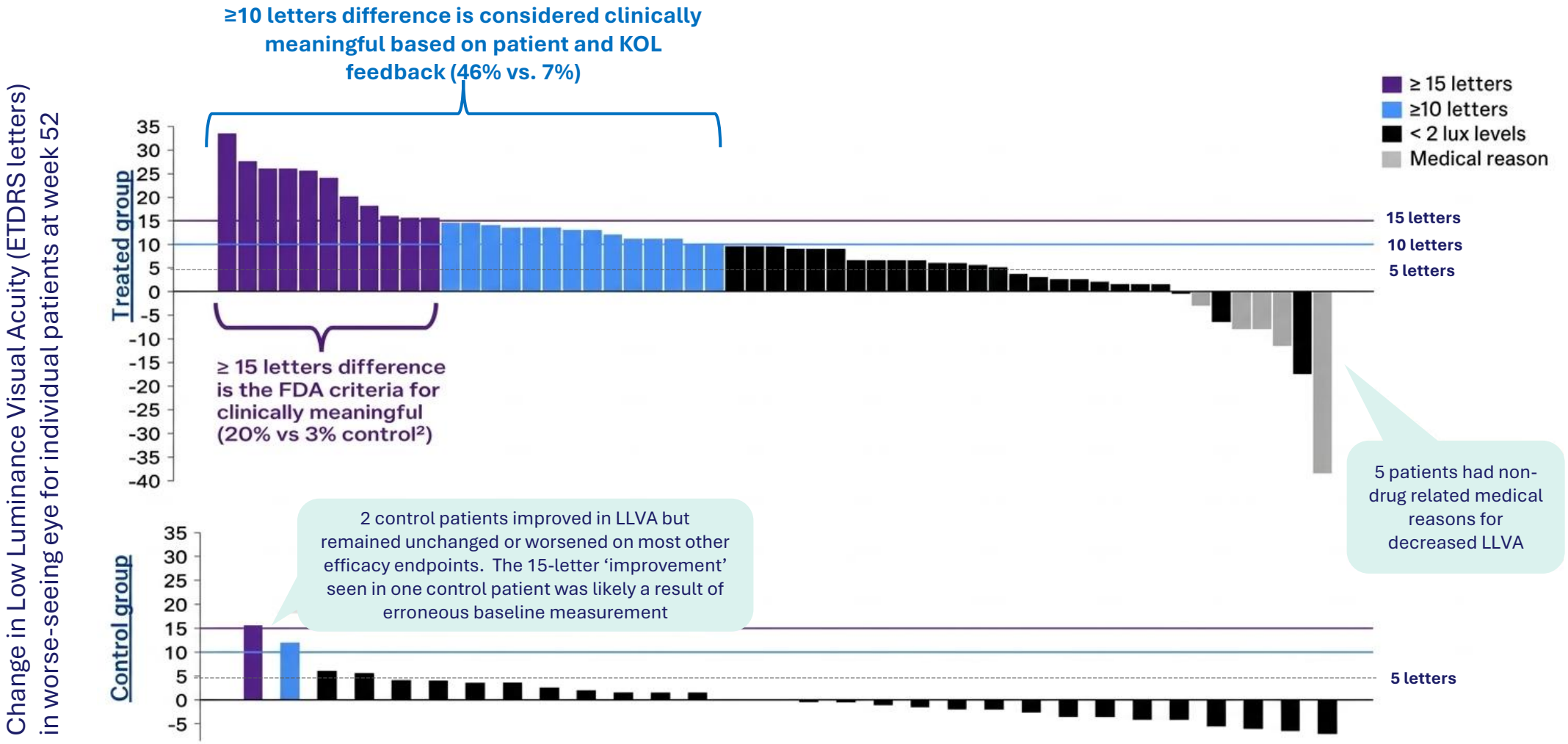
- **IVI-A:** significant improvement in total score vs. control at week 52 (**p=0.024)** with greater significance in the emotional well being questions (**p=0.005**)

- **Modified Low Luminance Questionnaire MLLQ** showed statistically significant improvement (**p=0.006)** with improvements in questions relating to mobility (**p= 0.001**), general dim lighting (**p= 0.007**) and emotional distress (**p= 0.019**) being highly significant

- **Notable concordance** between PRO interviews and other clinical data

MEIRAGTx

Impressive results for Visual Acuity measured in low light levels (LLVA) with 46% of treated patients achieving ≥10 letter gain on ETDRS chart compared to 7% for untreated controls

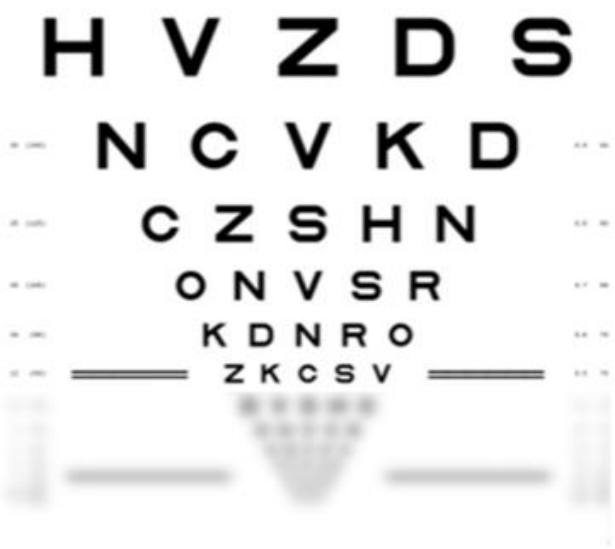


MEIRAGTx

Illustrative Depiction of Effect of bota-vec Treatment: 15 letters = 3 lines on the ETDRS chart

Before bota-vec

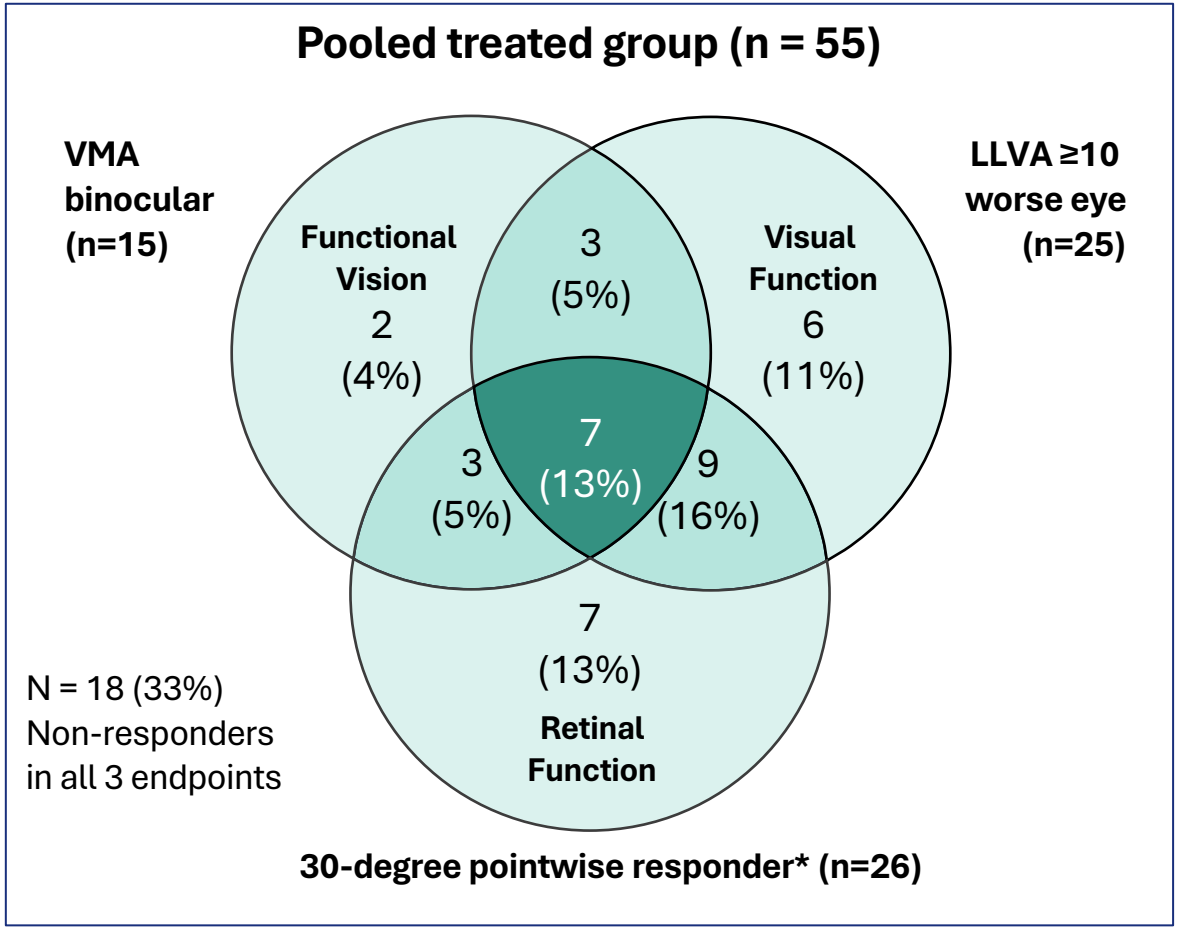
After bota-vec

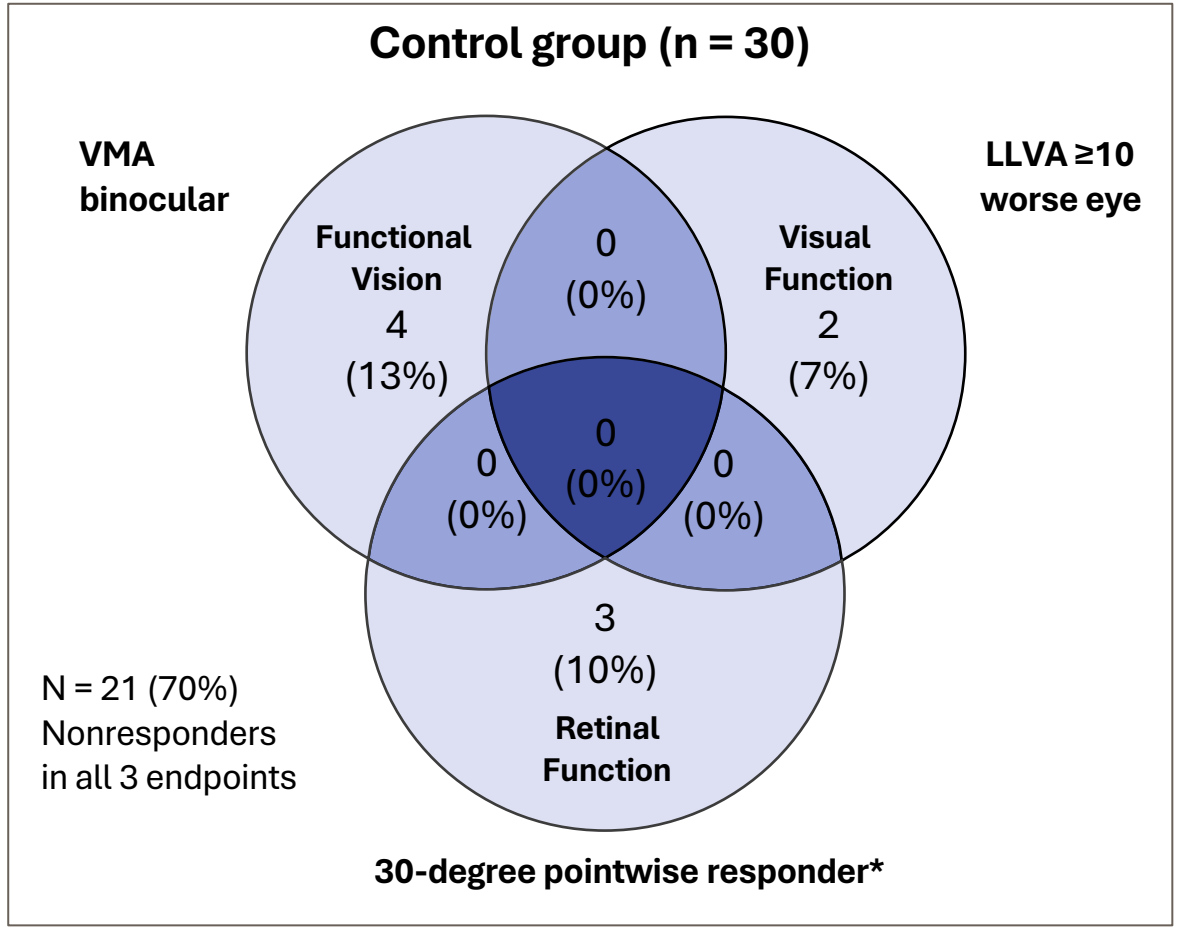


- 15 letters is equivalent to 3 lines on the eye chart
- From a functional standpoint in everyday life, a 3-line improvement in visual acuity means **you can now stand twice as far away from an object and still see it clearly**

- **Example of 15 letter visual acuity improvement from 0.8 logMAR or 20/125 (left image) to 0.5 logMAR or 20/60 (right image)**

40% (22/55) of Treated Patients Showed Improvement in ≥2 Endpoints Compared to 0% in Controls





MEIRAGTx

*Pointwise responder based on both eyes modeled analysis
LLVA, low luminance visual acuity; n, number; VMA, vision-guided mobility assessment.

Multi-Endpoint Responder Analysis: Comprehensive Results

FF = Full Field; Pt = Pointwise; binoc = binocular.

Consistent 25–40% treatment benefit across ALL endpoint combinations with most combinations showing 0% response in control arm

SECTION 1: VMA + LLVA COMBINATIONS

ENDPOINT COMBINATION	TREATED	CONTROL	DIFF
VMA binoc. + LLVA binoc. (≥10)	40.0%	0%	+40.0%
VMA binoc. + LLVA worse eye (≥10)	27.3%	0%	+27.3%
VMA binoc. + LLVA binoc. (≥15)	29.1%	0%	+29.1%
VMA binoc. + LLVA worse eye (≥15)	25.5%	0%	+25.5%

SECTION 2: VMA + STATIC PERIMETRY

ENDPOINT COMBINATION	TREATED	CONTROL	DIFF
VMA binoc. + Pointwise 30° binoc.	32.7%	3.3%	+29.4%
VMA binoc. + Pointwise 30° worse eye	25.5%	0%	+25.5%
VMA worse eye + Pointwise FF binoc.	30.9%	0%	+30.9%
VMA worse eye + Pointwise FF worse eye	29.1%	0%	+29.1%

SECTION 3: LLVA + STATIC PERIMETRY

ENDPOINT COMBINATION	TREATED	CONTROL	DIFF
LLVA worse eye (≥10) + Pt 30° binoc.	43.6%	3.3%	+40.3%
LLVA binoc. (≥10) + Pt 30° binoc.	36.4%	6.7%	+29.7%
LLVA worse eye (≥10) + Pt FF binoc.	41.8%	3.3%	+38.5%
LLVA binoc. (≥15) + Pt 30° worse eye	29.1%	0%	+29.1%

Conclusions

- Large Phase 3 study, 32 leading global sites (n=95). Although the novel primary endpoint was not statistically significant, there was a positive trend with the treated group 2.4x more likely to respond than untreated.
- Unprecedented clinically meaningful and statistically significant **improvements** were observed in **all three domains of vision (i)** retinal function (static perimetry and microperimetry); **(ii)** functional vision under low luminance (mLLO); and **(iii)** visual function (LLVA). Prior to studies with AAV-RPGR, stabilization of vision was expected and by regulators, this sort of strong improvement across all lines of vision was not previously known to be possible.
- Safety profile of bota-vec was as expected and manageable, no new safety signals in the Phase 3 with improved inflammatory profile and reduced surgery related A/Es.
- Supported by Phase 1/2 dose escalation and expansion study (n=43) for safety and efficacy.
- The Phase 3 study investigators strongly support seeking regulatory approval for bota-vec globally, signing an open letter from the Foundation for Fighting Blindness (FFB)

MEIRAGTx

*VMA is a novel assessment first used in this study.
bota-vec, botaretigene sparoparvovec; RPGR, retinis pigmentosa GTPase regulator; VMA, vision-guided mobility assessment.

MEIRAGTx

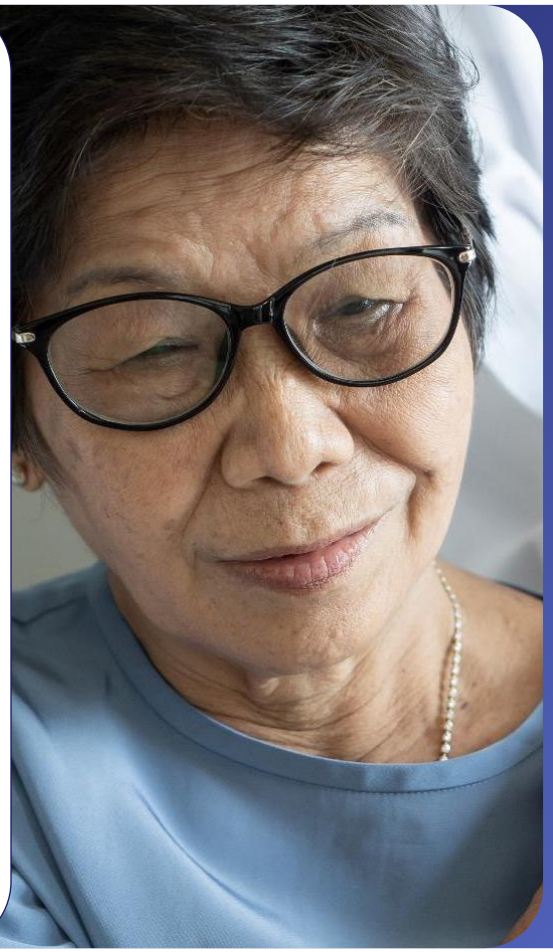
AAV-GAD: a first-in-class genetic medicine for treatment of Parkinson's disease

Phase 3 ready | evidence of disease modification | RMAT designation

Parkinson’s Disease

AAV-GAD overview

- Parkinson’s disease (PD) is the second most common neurodegenerative disease
- Approximately one million patients in the U.S. currently living with Parkinson's disease
- Individuals with PD initially respond to dopamine replacement therapy; however, over time, most patients become inadequately controlled by therapy or suffer from treatment-related complications
- **AAV-GAD is designed to locally deliver GABA, a neurotransmitter that can help restore normal brain circuitry in any form of Parkinson’s disease**
- **AAV-GAD has been tested in 58 patients across three clinical studies and is the only cell or gene therapy in PD to meet the prespecified primary endpoint in two randomized, double-blind, sham surgery-controlled trials**
- Granted RMAT designation by FDA – providing benefits of both Fast Track and Breakthrough Therapy designations



10M

Parkinson’s patients worldwide

$52B

Estimated economic burden of PD in the US

AAV-GAD: a first-in-class therapy for Parkinson's Disease

Therapeutic Approach

AAV-GAD delivers the Glutamic Acid Decarboxylase (GAD) gene locally into the sub-thalamic nucleus (STN)

GAD converts glutamate (excitatory neurotransmitter) to GABA (inhibitory neurotransmitter) to alleviate PD-associated hyperexcitation of circuitry controlling movement

- **Localized delivery of AAV-GAD directly into the STN**
  avoids safety risks associated with high dose/broad exposure of AAV in CNS. No safety signals in any studies
- **Standard and brief surgical procedure (same target site as DBS)**
  no need for general anesthesia, well-known surgical route for administration
- **One-time therapy**
  Post infusion no further intervention and no frequent follow-ups for tuning stimulation required

The Glutamic Acid Decarboxylase (GAD) gene is delivered locally to the STN.

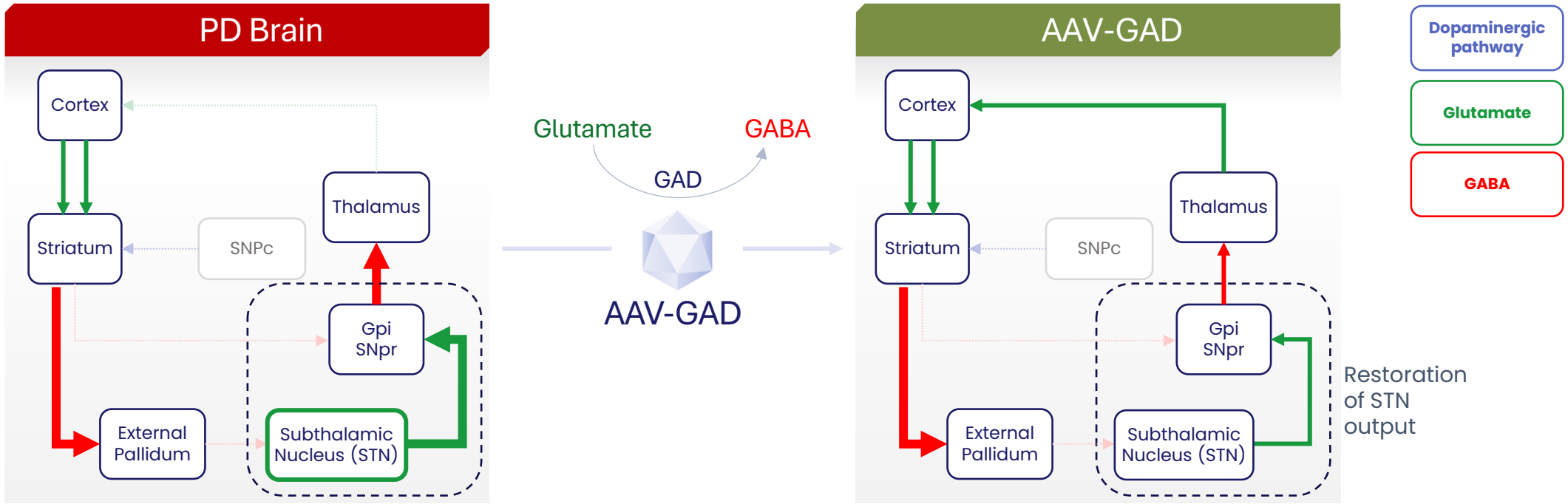
Conversion of glutamate to GABA via GAD normalizes GABA levels in the STN and at STN targets alleviating PD-related motor symptoms

Status: Phase 3 Ready

- **Positive clinical data from three clinical studies:**
  - Phase 1: unilateral, dose escalation study
  - Phase 2: bilateral, sham-controlled study
  - Sham-controlled bridging study using GMP material manufactured using commercial ready process in-house at MeiraGTx
- **Phase 3 ready – commercial ready drug product released early 2026**

Mechanism of action

AAV-GAD circumvents need for dopamine input to suppress STN hyperactivation, resulting in improved motor function



- In PD, loss of dopaminergic neurons in the substantia nigra (SNPc) results in decreased GABA input to the STN
- As a result of decreased GABA input, the STN is hyperactivated
- This results in uncontrolled activation of the basal ganglia output nuclei (GPi, SNpr), which then act to continually repress the activity of the thalamus – leading to the motor symptoms of PD

- **AAV-GAD, delivered directly to the STN, results in conversion of glutamate (excitatory neurotransmitter) to GABA (inhibitory neurotransmitter) locally in the STN**
- **Increased GABA and reduced glutamate output of the STN, releases the GPi and SNpr inhibition of the thalamus, leading to restored cortical activity and improved motor function**
- **Self-limiting autoregulation:** STN neurons express $GABA_A$ receptors, which inhibit further release of GABA upon increase in extracellular GABA levels

Results from a Phase 1, dose escalation study of AAV-GAD

Study design

Single-arm, open-label, dose escalation study of **unilateral** subthalamic administration of AAV-GAD in patients with PD (n=12)

Safety

- AAV-GAD was generally safe and well tolerated, with no adverse events related to the therapy
- No abnormalities were noted on postsurgical MRIs up to 1 year
- No evidence of adverse events in the perioperative period and for at least 1 year after treatment (most patients followed up for >2 years)
- No evidence of vector-related immunity

Efficacy findings

- Significant improvements in motor UPDRS scores, predominantly on the side of the body contralateral to surgery, were seen as early as 3 months after therapy and persisted to 12 months (latest follow-up)
- PET scans revealed a substantial improvement in thalamic metabolism that was restricted to the treated hemisphere
- Correlation found between clinical motor scores and brain metabolism in the supplementary motor area

Kaplitt MG et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet. 2007;369:2097-2105

Results from a Phase 2, randomized, double-blind, sham-controlled, multi-center study of AAV-GAD

Study design

- Randomized (n=45, 1:1) double-blind study of bilateral STN AAV-GAD against sham control in patients with advanced Parkinson's Disease
- Primary endpoint: change in off-medication UPDRS Part 3 score at 6 months between treated and sham

Safety

- AAV-GAD was generally safe and well tolerated with no SAEs related to the therapy
- Other adverse events were mild or moderate, likely related to surgery and resolved
- Worsening of PD was reported in 35% of sham patients vs. 0% of AAV-GAD, further supporting efficacy
- No difference in neuropsychological, speech and depression ratings

AAV-GAD is the only interventional gene or cell therapy study in PD to meet the primary clinical endpoint in a sham-controlled study

Efficacy findings (summary):

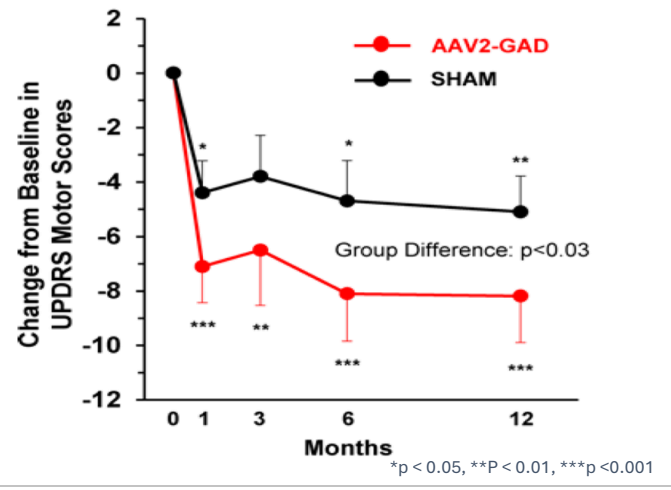
- **Study met primary endpoint: UPDRS 3 motor score improvements were significantly greater in the AAV-GAD treated group vs. sham at 6 months; Improvements persisted at 12 months**
- Significantly greater responder rate in AAV-GAD treated group (50%) compared with sham (14.3%)
- Improvements in secondary outcome measures, including ON time across 12 months (no change in sham at any time point)
- Significant reduction in medication complications at 6 and 12 months (UPDRS 4) in AAV-GAD group (vs. no change in sham at any point)
- FDG-PET imaging showed significant changes in brain motor networks of AAV-GAD subjects not observed in the sham group

MEIRAGTx

LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurology. 2011; 10(4):309-19.
Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133.

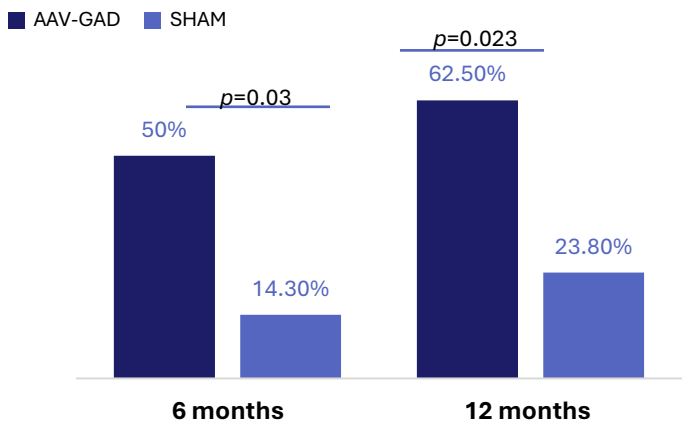
Results from the Phase 2 study: significant improvements following AAV-GAD treatment compared to sham surgery control

Significant improvements in UPDRS 3 motor scores



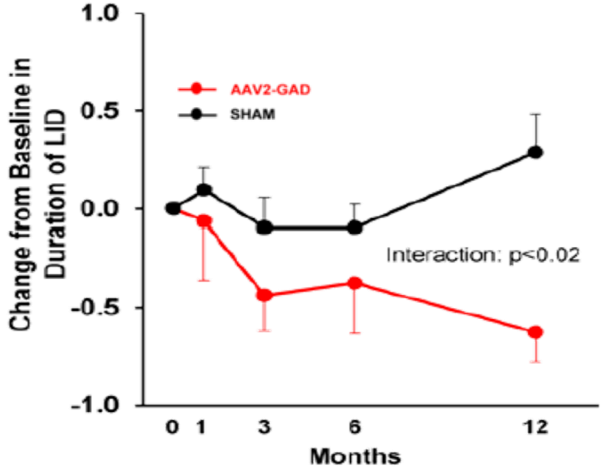
- **Met primary outcome measure: improvement in UPDRS 3 motor scores vs. sham at 6 months**
- Improvements in the AAV-GAD group were observed at all time points

Significantly greater responder rate ≥9 points UPDRS



- A 9.0 point improvement in UPDRS motor score corresponds with a 25% improvement from average baseline score
- **Significantly greater responder rate was observed in the AAV-GAD group (50%, 8/16) vs. sham group (14%, 3/21) at 6 months and 12 months (10/16 vs. 5/21 patients)**
- 7/8 subjects in the AAV-GAD group who were classified as responders at 6 months, remained responders at 12 months (vs. only 1 of 3 subjects in the sham group)

Reduction in duration of levodopa-induced dyskinesia



- **Significant improvement in drug-induced dyskinesia at 12 months relative to baseline in the AAV-GAD group (vs. no change in the sham group)**

MEIRAGTx

LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. Lancet Neurology. 2011; 10(4):309-19.
Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133

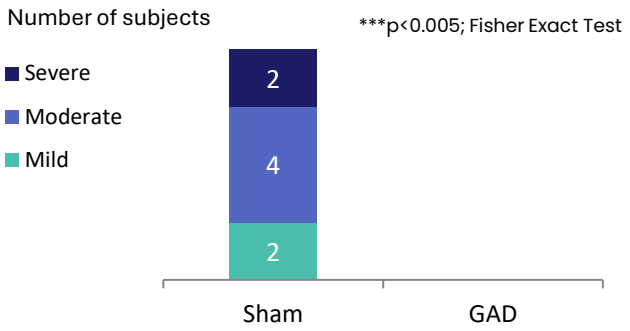
AAV-GAD treatment is safe & well tolerated

Worsening of Parkinson's observed in sham group but not in AAV-GAD treated group

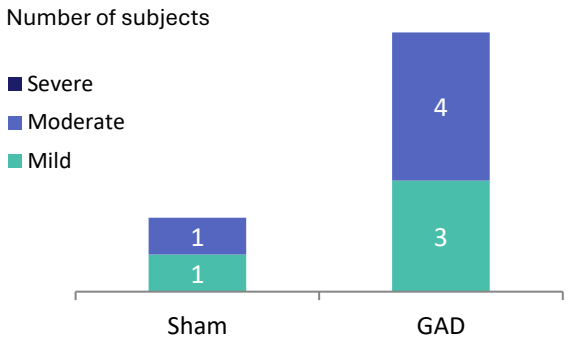
Adverse events over 12 months (20% or greater frequency)

- **Worsening of Parkinson's Disease occurred in 8 sham subjects but was not reported for any AAV-GAD subject, further supporting efficacy outcomes in the AAV-GAD group**

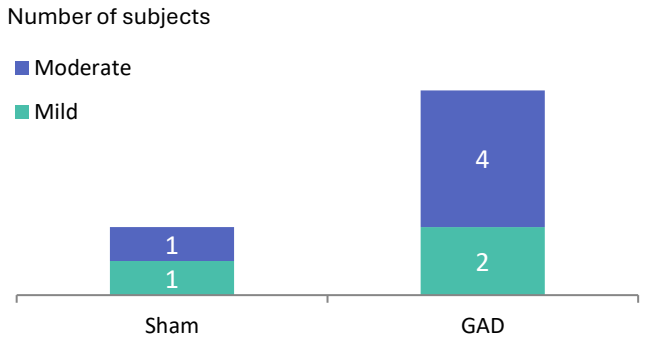
Worsening of Parkinson's Disease



Headache



Nausea



Serious Adverse Events

Number of subjects

	Sham	GAD
Intestinal obstruction		1
Accidental drug overdose		1
Prostatitis		1
Delusion, Hallucination Parkinson's Disease worse	1	

AAV-GAD therapy shows evidence of disease modification

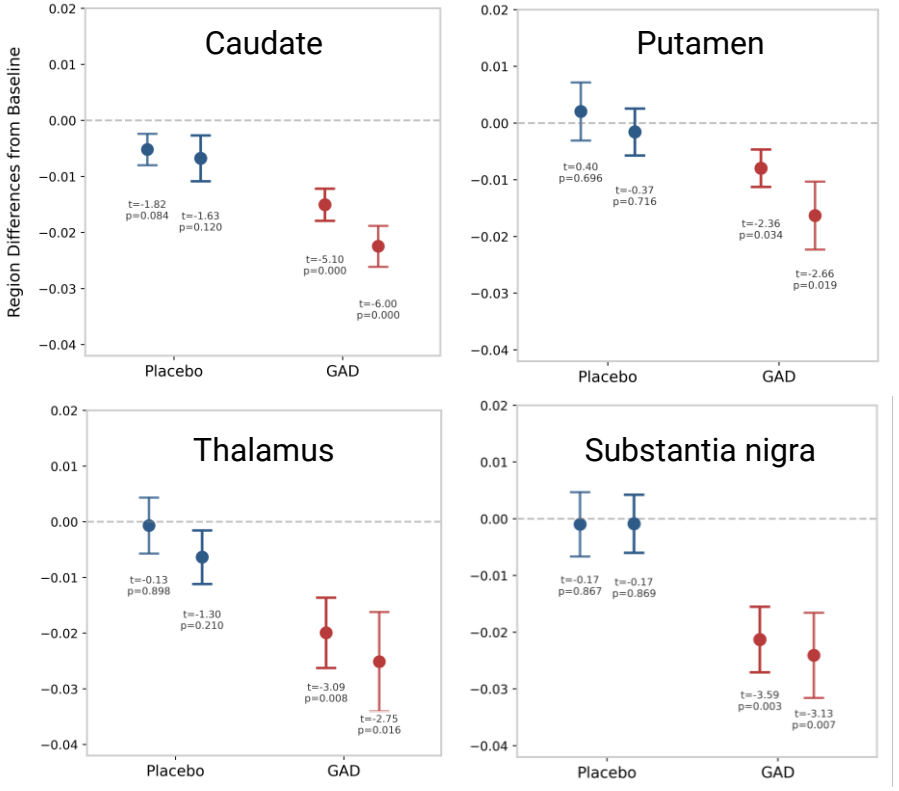
Disease modification in preclinical models[1]

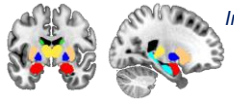
- Preclinical studies in animal models of PD have shown that treatment with AAV-GAD directly into the STN not only normalizes the function of the STN but also leads to consequent reduction in the pathological hyperexcitation of the downstream basal ganglia and the substantia nigra
- **These experiments also demonstrated a significant neuroprotective effect in the substantia nigra, increasing the survival of dopaminergic neurons i.e., physiologically slowing the progression of the disease**

Evidence of disease modification from clinical studies

- Comparison of blinded FDG-PET data from sham and treated patients in the double-blind sham controlled AAV-GAD clinical studies has shown significant reduction in the activity of critical basal ganglia regions known to be hyperexcited in PD
- **This demonstrates a disease-modifying effect on the pathological circuitry of the brain that underpins the clinical manifestations of PD**
- **In addition, FDG-PET analysis has shown reduction in pathological hyperexcitability within the substantia nigra**, confirming the observations in animal studies, exerting a neuroprotective effect with the potential to reduce the rate of dopaminergic loss
- **No other treatment in PD has shown such potentially disease modifying effect**

FDG-PET data from AAV-GAD clinical trials shows disease-modifying effects in the basal ganglia circuitry, including the substantia nigra – the site of dopamine-producing neurons affected in PD





In collaboration with

HOLOGEN AI

MEIRAGTx

1- Luo J, Kaplitt MG, Fitzsimons HL, et al. Subthalamic GAD gene therapy in a Parkinson's disease rat model. Science. 2002;298(5592):425-429.

Positive topline data summary from AAV-GAD sham surgery-controlled Bridging Study

A 6-month, three-arm, randomized, double-blind, sham-controlled study using material manufactured in-house at MeiraGTx

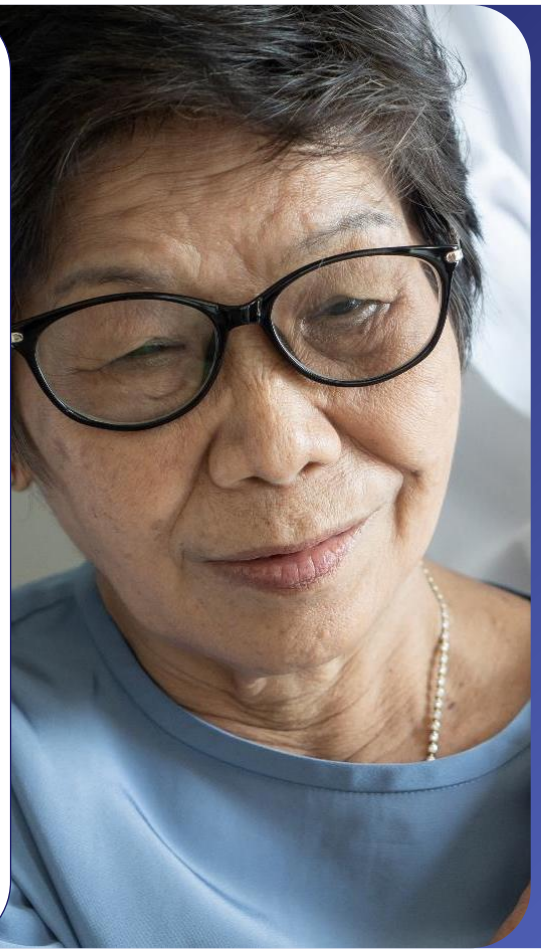
- 14 subjects were randomized to one of three groups receiving bilateral STN AAV-GAD infusions: low dose group (3.5×10^{10} vg per STN, n=5), high dose group (10.5×10^{10} vg per STN, n=5) and sham control (n=4)
- AAV-GAD Drug Product was manufactured at MeiraGTx using its commercial platform process at its wholly-owned facilities

Summary of results:

- **AAV-GAD was generally safe and well tolerated with no serious adverse events related to AAV-GAD treatment**
- **Significant, clinically meaningful improvements demonstrated in AAV-GAD treated subjects for key efficacy endpoints**
- **At Week 26, a statistically significant 18-point average improvement from baseline in UPDRS part 3 "off" medication score was demonstrated in the high dose group (p=0.03), with no significant change in the sham or low dose groups**
- **Significant improvement from baseline in the disease-specific, patient-reported quality of life PDQ-39 score was demonstrated in both the high and low dose groups with no change in the sham group at Week 26**
- For more information on the AAV-GAD bridging study, please see press release here

Summary: AAV-GAD for treatment of Parkinson's disease

- **AAV-GAD is the only CNS gene therapy program tested in three human trials – meeting a prespecified efficacy primary endpoint**
  - A total of 58 patients in 3 independent multicenter clinical studies received AAV-GAD treatment
  - AAV-GAD was safe and well tolerated in all doses tested, with no treatment-related SAEs
- **The only CNS gene therapy program with two randomized, double-blind, sham surgery-controlled trials which met prespecified primary endpoint**
- **Evidence of disease modification – from blinded FDG-PET imaging from the sham controlled clinical studies supported by data frompreclinical models**
- **Granted RMAT designation in 2025**
- **Program status: Phase 3 ready**



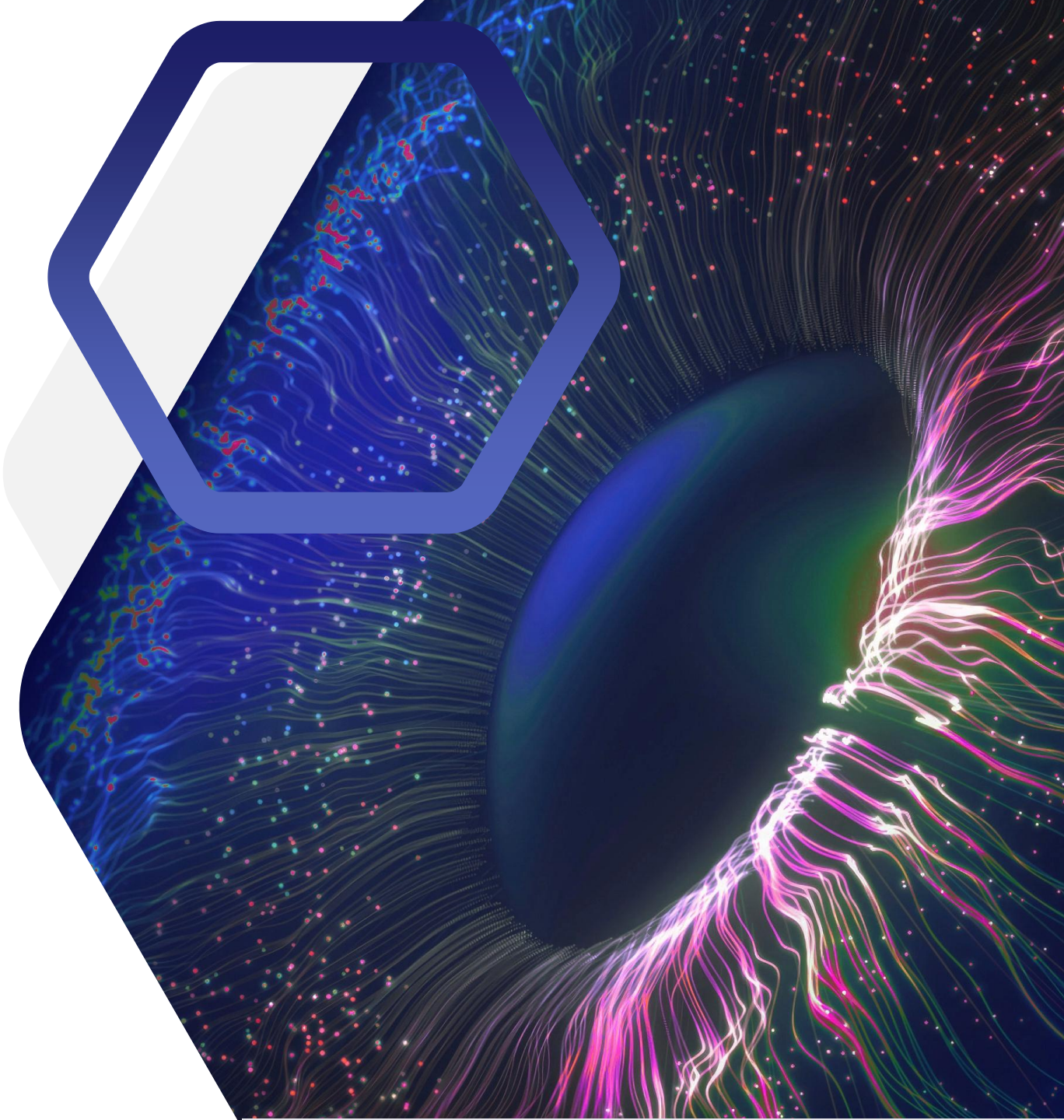
- ☑ Large market with high unmet need in patients no longer responding to dopamine therapy
- ☑ One-time treatment; standard surgical procedure, short OR time, no need for general anesthesia
- ☑ One time local delivery of AAV – safety and low COGS
- ☑ Internally manufactured by MeiraGTx using commercial-ready, high yield process

MEIRAGTx

AAV-AIPL1 for treatment of AIPL1-associated retinal dystrophy[1]

Restoring vision in children who are born legally blind

Potential Path to Marketing Authorization under exceptional circumstances | RPDD, Orphan Drug Designation in US & EU



[1] Partnered with Eli Lilly

AIPL1 video

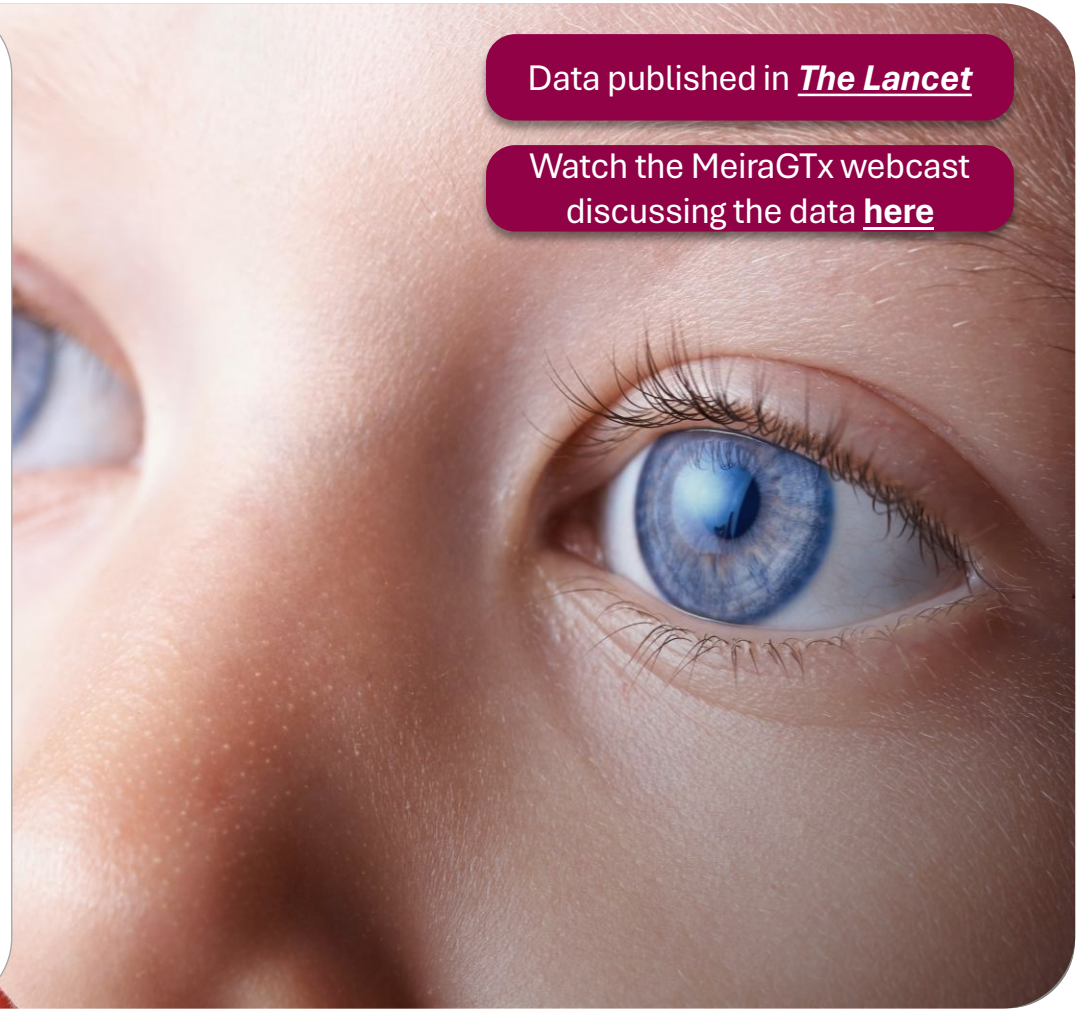
Click to play video

AAV-AIPL1 for treatment of LCA4 retinal dystrophy[1]

Potential path to marketing authorization in UK and US

A novel treatment for AIPL1 congenital blindness

- Children with AIPL1-associated retinal dystrophy (LCA4) are blind from birth. By age 4, retinal degeneration is complete and irreversible
- There are currently no approved treatments for AIPL1-LCA4
- **Clinical data from 11 children demonstrated transformative efficacy[2]: 100% of treated children, who were legally blind from birth, now have visual acuity with benefits seen as early as one month following treatment**
- The visual improvements in all 11 children have also resulted in life-changing benefits in all areas of development, including communication, behavior, schooling, mood, psychological benefits and social integration
- AAV-AIPL1 treatment was generally safe and well tolerated with no treatment-related SAEs
- **These improvements are unrivalled in treatment benefit compared to any other ocular therapy, including any approved or published ocular gene therapy**
- **Potential near-term path to marketing approval in UK and US**



Data published in ***The Lancet***

Watch the MeiraGTx webcast discussing the data **here**

MEIRAGTx

[1] Partnered with Eli Lilly

2- Michaelides, M., Laich, Y., Wong, S. C., Georgiadis, I., Moosajee, M., Lanza, R., Ali, R. R., & Saper, V. (2025). Gene therapy in children with AIPL1-associated severe retinal dystrophy: an open-label, first-in-human interventional study. The Lancet, 405(10479), 648–657.

MEIRAGTx

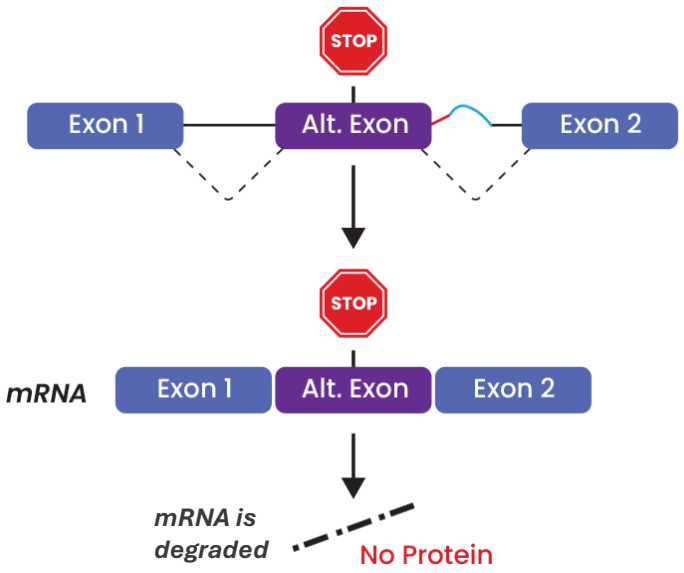
Riboswitch Gene Regulation Platform

In vivo production of vectorized therapeutic proteins and peptides with oral inducers

Riboswitch platform: precise *in vivo* production of therapeutic proteins via oral small molecule inducers

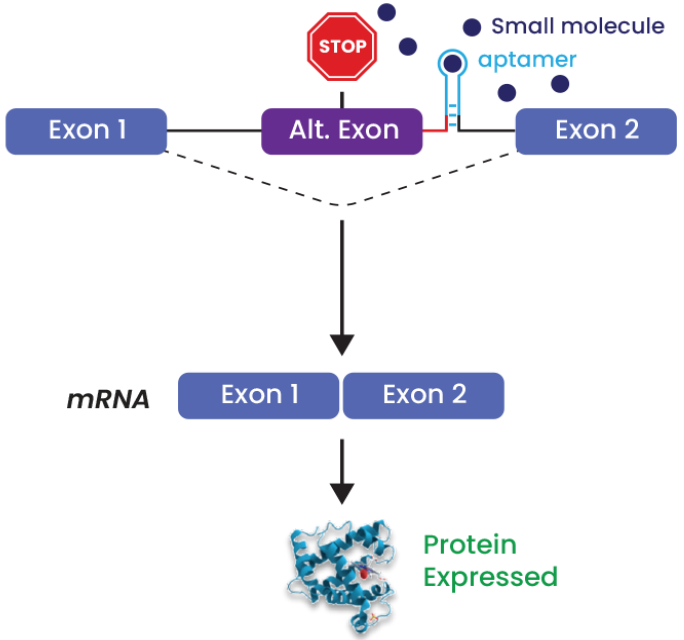
mRNA formation is controlled by alternative splicing cassette via binding of a small molecule inducer to the Riboswitch cassette

No small molecule (OFF state)



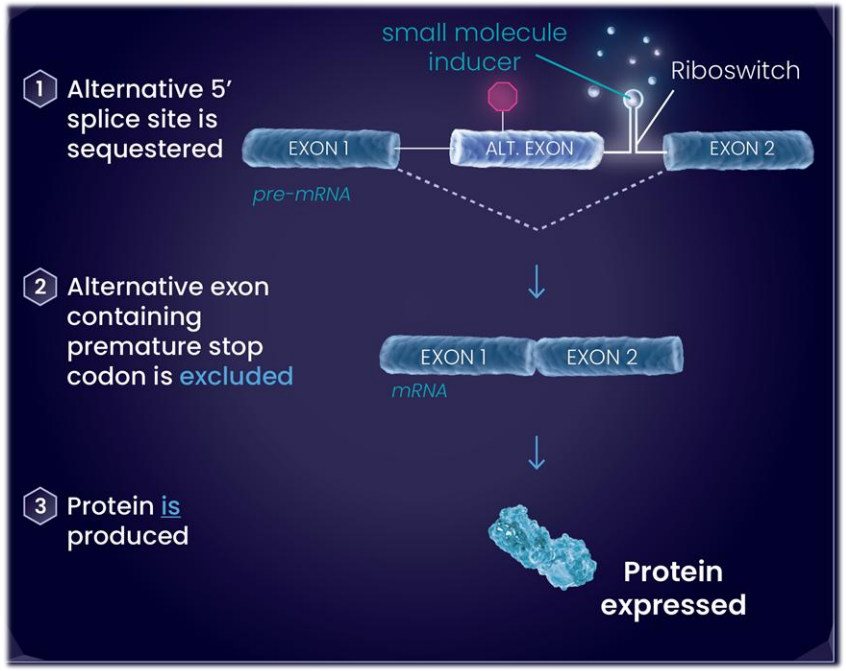
In the absence of the small molecule inducer ("OFF state"), the incorporation of an alternative exon with a premature stop codon drives degradation of the mRNA transcript via the ubiquitous process of nonsense-mediated decay (NMD)

With small molecule (ON state)



Binding of the small molecule inducer to the Riboswitch aptamer drives stabilization of a hairpin structure which incorporates the 5' splice site of the second intron, triggering splicing out of the alternative exon and production of a stable, protein-encoding transcript

Riboswitch provides significant advantages over other inducible systems



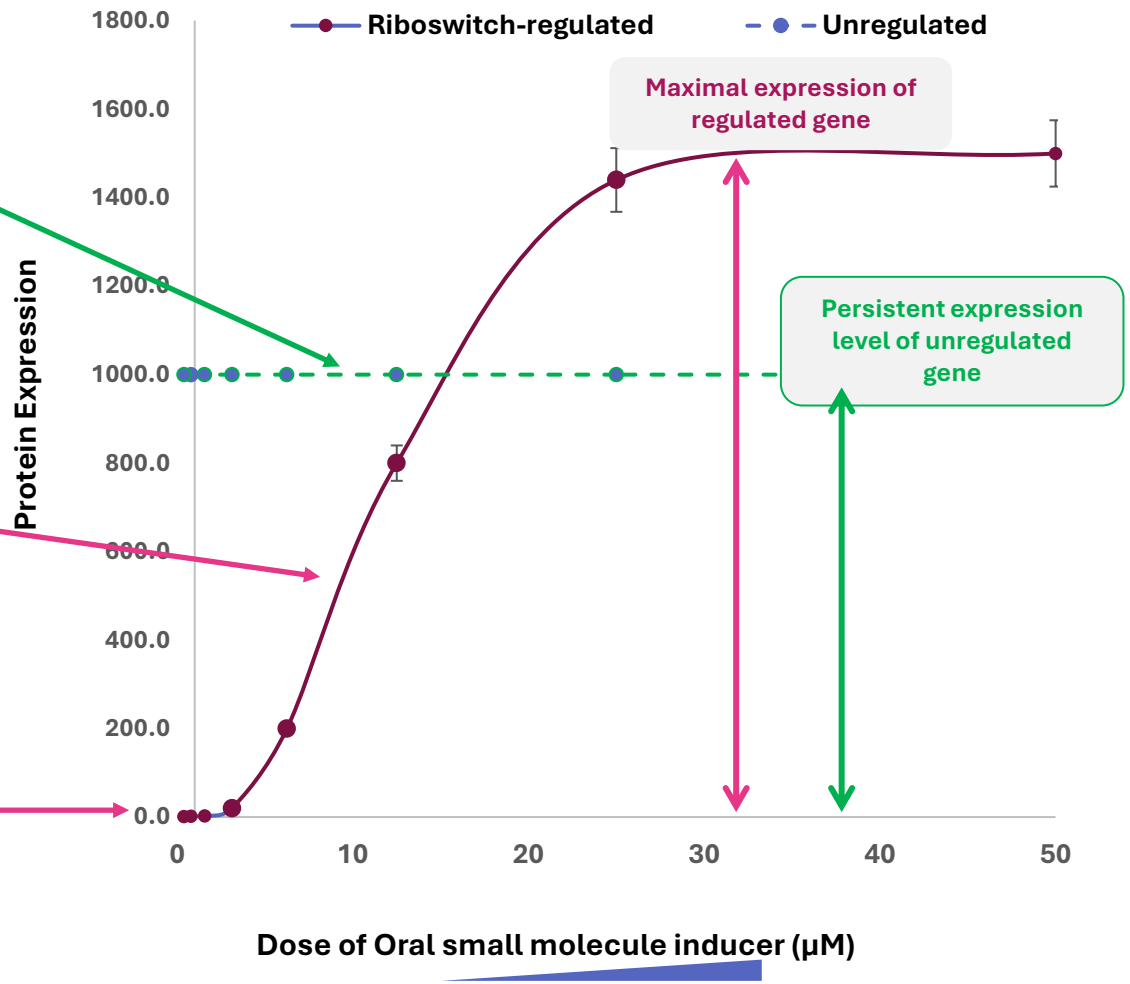
- The native form of any biologic therapeutic can be encoded by the DNA template and produced *in vivo*, controlled by bespoke oral small molecules
- Extremely precise dosing of biologic therapeutics with the production of the therapeutic protein dependent on the oral small molecule inducer pharmacodynamics (PD)
- Dosing of native form of therapeutic results in same properties and function as the endogenous protein or peptide: i.e.: crosses the BBB and acts on CNS receptors
- Pulsatile delivery of naturally short-lived peptides results in more physiological function with improved efficacy and reduced side effects - in contrast to infrequent high doses of synthetic long-lasting peptides.
- Durability of biologic therapeutic production and maintenance of efficacy, PD and dynamic range demonstrated for greater than a year in murine models
- DNA template be delivered via any vector (viral or non- viral), *ex vivo* or *in vivo*

Riboswitch splicing cassette drives precise control of therapeutic protein production with unprecedented dynamic range and precision

Expression level of the gene construct without the Riboswitch cassette is independent of small molecule dosing

Expression of Riboswitch containing transgene in precise dose response to the oral small molecule inducer dose

Basal expression of regulated construct without small molecule inducer



Riboswitch regulated gene expression:

- Precise dose response to oral small molecule dose
- Basal level with no small molecule undetectable
- Maximum expression higher than the identical gene construct lacking the Riboswitch cassette – splicing event drive mRNA efficiency and stability improving protein production

A broad range of therapeutic proteins encoded by Riboswitch-containing transgenes show tight control via oral small molecule dosing, *in vivo*

Therapeutic Antibodies

- Anti-PCSK9
- Anti-VEGFR2 (eye)
- Anti-Amyloid
- Anti-IL-17
- Anti-PD1
- Anti-HER2
- Anti-IL4Ra
- Anti-Myostatin

Cell Therapy

Ribo-CAR:

- Anti-CD19
- Anti-PSMA
- Anti-mesothelin
- Anti-HER2

Therapeutic Hormones/Cytokines /Peptides

- Epo
- hGH
- PTH
- Insulin
- GLP-1R agonists
- Gut peptide combinations: GLP1- GIP; GLP1, GIP, PYY, Glucagon, Amylin, Oxyntomodulin
- Myokines
- Adipokines e.g: leptin

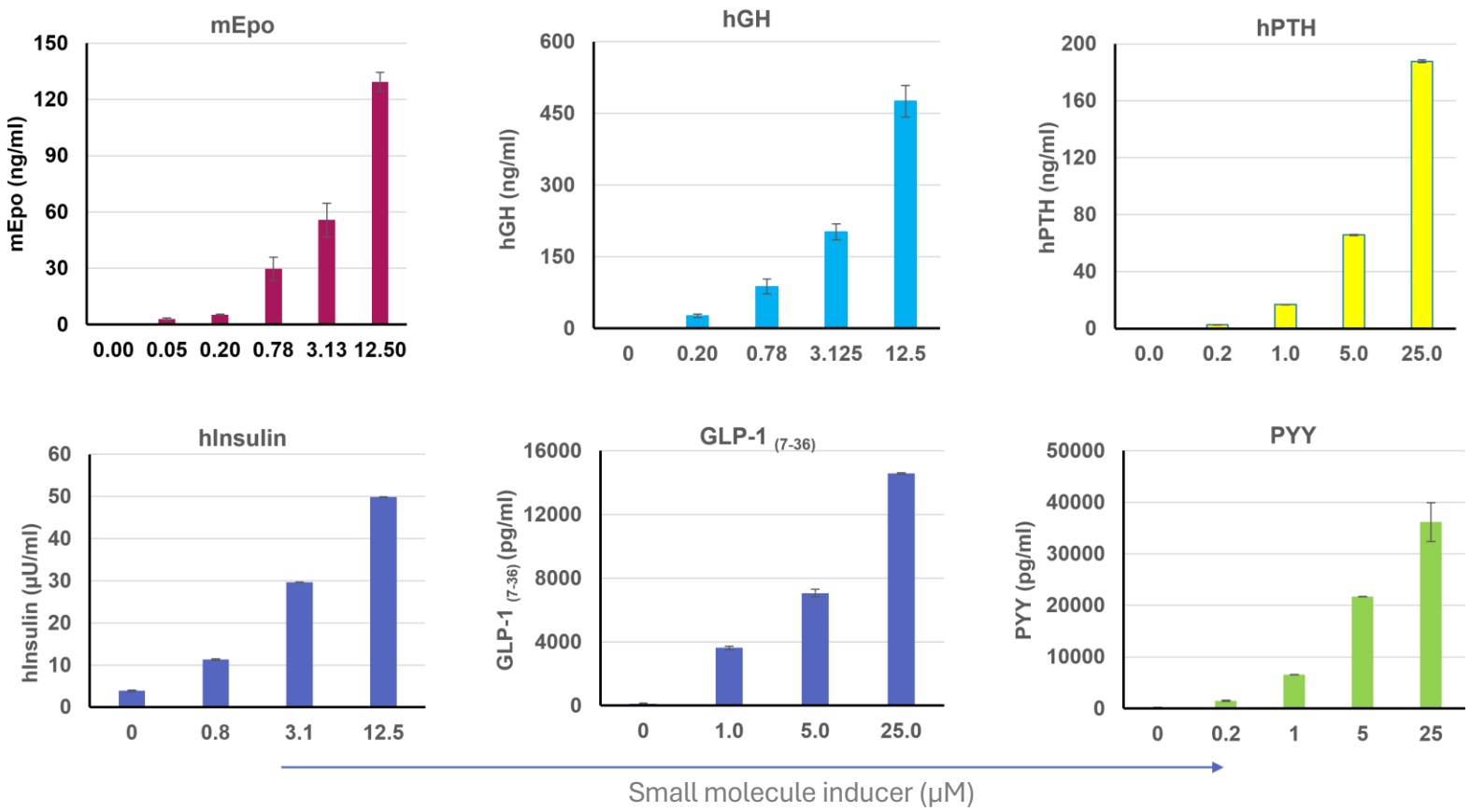
Gene/RNA Editing Nucleases

- Cas9
- CasRx

Precise regulation of multiple therapeutic hormones and peptides with riboswitch, *in vitro*

The riboswitch platform can be applied to any transgene and delivered by any vector - achieving *in vivo* production of the therapeutic protein or peptide in a precise dose response to a bespoke orally administered small molecule inducer.

- Graphs to the right show examples of regulation of human hormones in response to dosing with a small molecule riboswitch inducer, *in vitro*
- Many of these targets have been validated in relevant animal models, showing precise control of therapeutic protein serum levels and therapeutic effect driven by the dose of the oral small molecule inducer



MEIRAGTx

Riboswitch regulation of metabolic peptides, alone or in combination

In vivo production of natural gut peptides

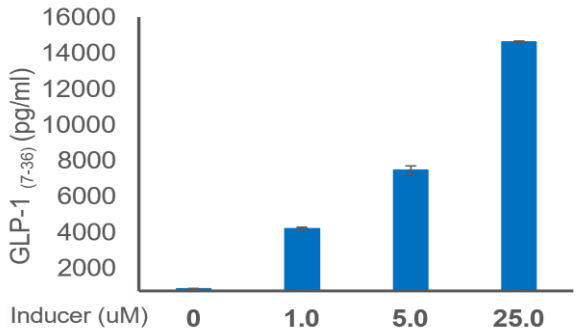
- Delivery of high effective levels of active peptides can be challenging. MeiraGTx has achieved high expression of natural gut peptides, alone or in combination produced by the oral dosing of a small molecule activator
- The Riboswitch platform provides tight and controlled expression of unmodified, wild-type peptides
- Delivery of multiple combinations of peptides can be achieved using a single vector

These can be constructed and tested rapidly head-to-head to provide fast *in vivo* proof of concept of efficacy and benefit on **muscle mass, metabolism, and feeding as well as behavior and CNS impact**

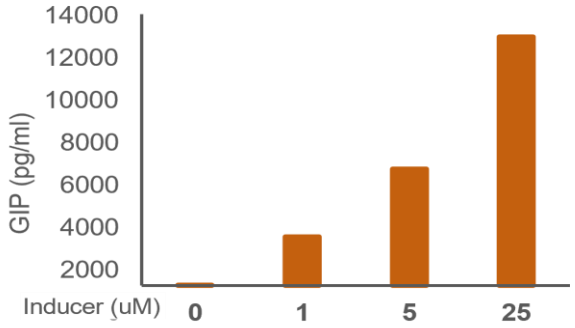
Single Peptide Constructs	Combination Peptide Constructs		
GLP-1	GLP-1	GLP-1	
GIP	GLP-1	GIP	
Glucagon	GLP-1	GLP-1	GLP-1
Oxyntomodulin	GLP-1	Glucagon	GIP
PYY	GLP-1	Oxyntomodulin	PYY
Amylin	GLP-1	Amylin	PYY
	GLP-1	GIP	PYY

Riboswitch regulation cassette controls the expression of combinations of gut peptides GLP-1, GIP and PYY, *in vitro*

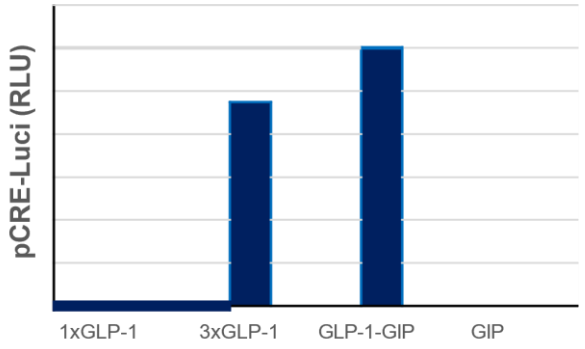
GLP-1 expression



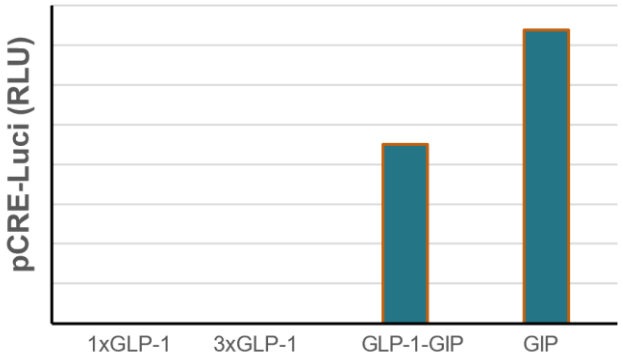
GIP expression



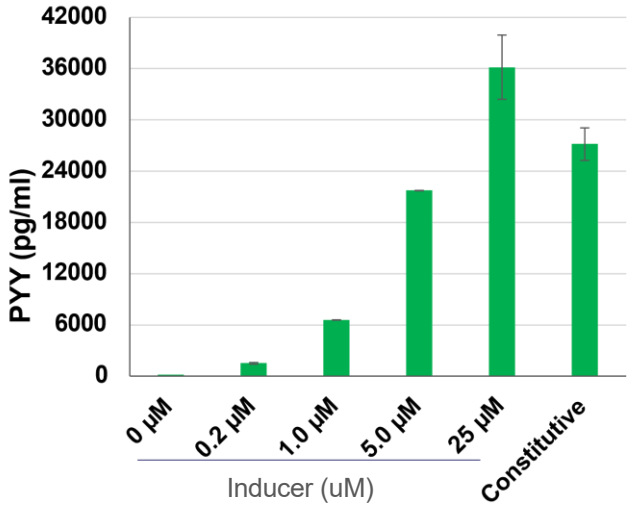
GLP-1 activity specifically on GLP-1 receptor



GIP activity specifically on GIP receptor



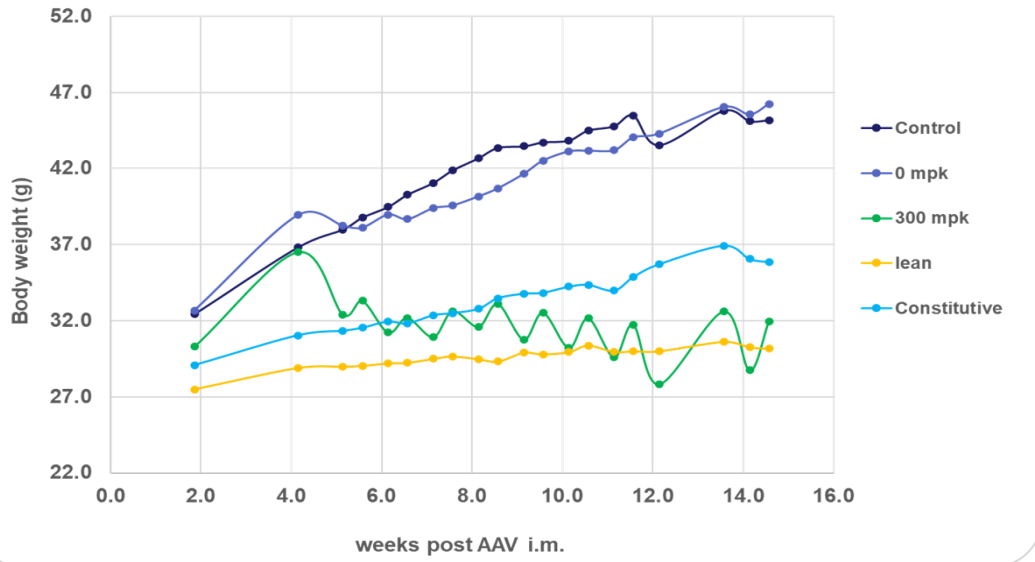
PYY expression



In vivo delivery of GLP1-GIP via daily oral inducer dosing significantly improves weight loss and glucose control compared to constitutively expressed GLP1-GIP

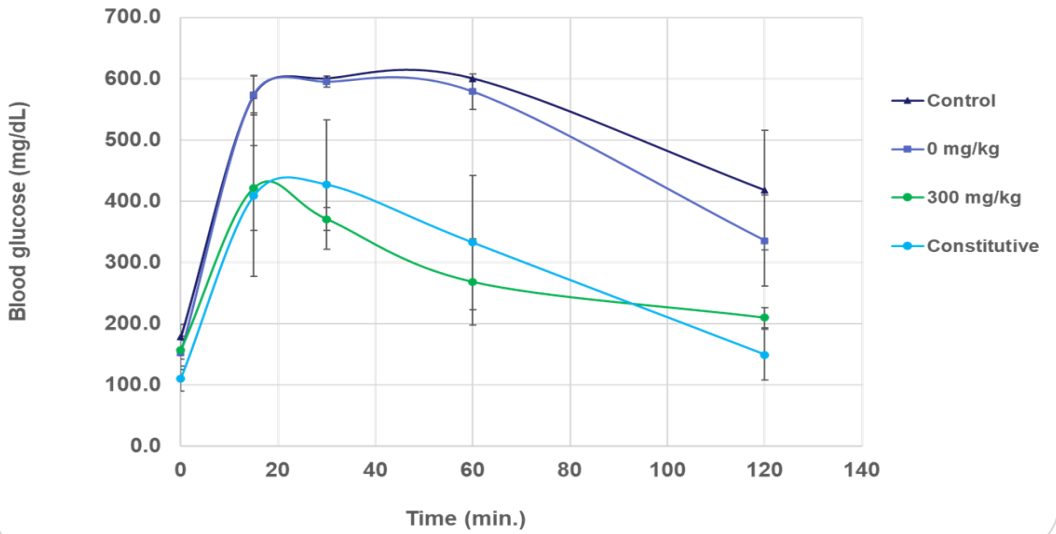
GLP1-GIP: comparison of constitutive expression of the dual peptides compared to daily *in vivo* delivery induced by oral small molecule

Weight loss in DIO mice



- Untreated DIO mice gain weight persistently over the 15 weeks of the experiment (dark blue line). Expression of GLP1-GIP from the constitutive vector (light blue line) results in weight reduction
- **Daily oral dosing of the small molecule (green line) results in rapid and persistent weight loss, with mice reaching lean weight (black line) 8-10 weeks after small molecule dosing has begun**
- **The "zig zag" line reflects the fact that the animals were only dosed on weekdays and not on weekends, indicating that in the absence of the small molecule, GLP1-GIP production diminishes; the native form of the peptide is expressed in a pulsatile fashion resulting in improved efficacy over time**

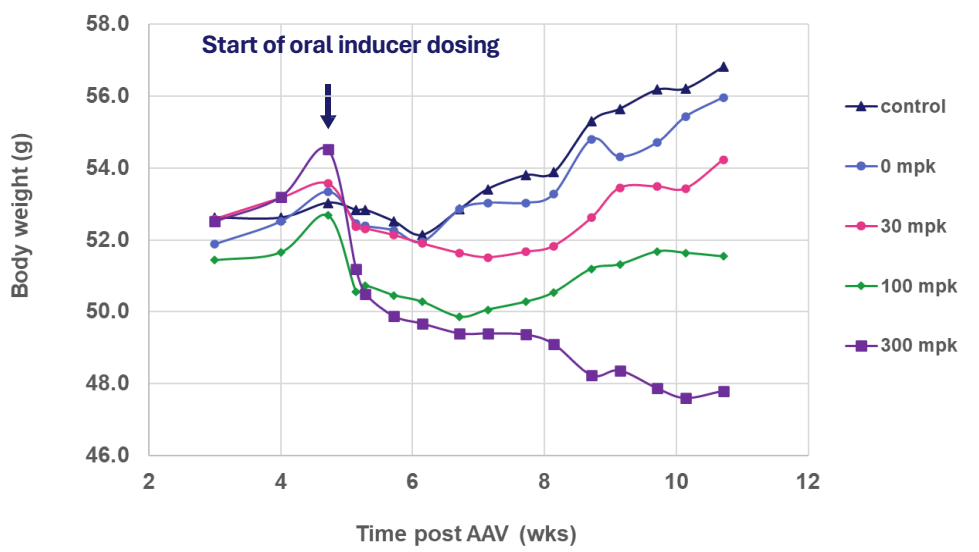
Glucose Control in DIO mice



- Control untreated DIO animals (green line) show poor glucose control following a glucose challenge
- No improvement in glucose control is observed in animals with the regulated GLP1-GIP construct in the absence of oral dosing of the small molecule (light blue line 0 mg/kg)
- Glucose control is clearly improved when GLP1-GIP is constitutively present (dark blue line)
- **Rapid glucose control is seen in animals receiving GLP1-GIP via daily dosing of the small molecule (pink line)**

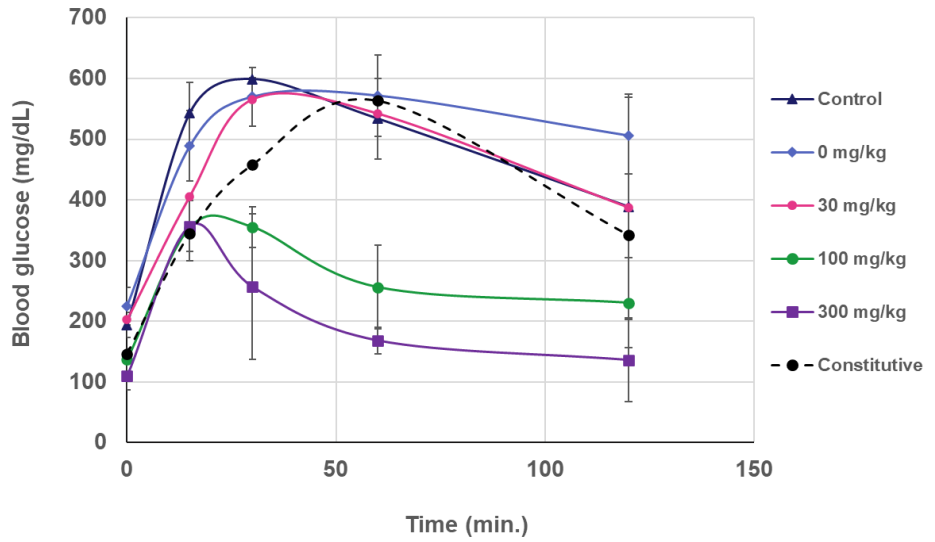
In vivo delivery of GLP1-GIP-Glucagon via daily oral inducer dosing significantly improves weight loss & glucose control vs. constitutive GLP1-GIP-Glucagon

Weight loss in DIO mice



- Untreated DIO mice show persistent weight gain over 10 weeks (black line - control)
- The regulated construct in the absence of the small molecule (blue line, 0 mg/k) shows no significant difference in weight gain from the DIO mice
- A 30 mg/kg and 100 mg/kg dose of the small molecule delivered orally daily (including weekends) resulted in weight loss in a dose dependent manner (pink and green lines)
- **When the oral small molecule dose was further increased (purple line) - persistent and significant weight loss was observed**
- In this experiment, animals received an oral dose of the small molecule every day, including weekends

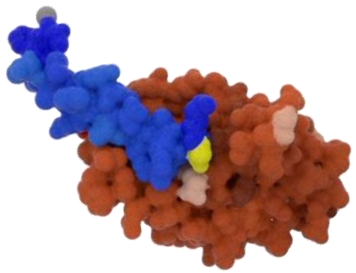
Glucose Control in DIO mice



- Untreated DIO animals show poor glucose control post glucose challenge (black line - control)
- The regulated construct in the absence of the small molecule (blue line, 0 mg/k) shows no difference from untreated DIO mice in glucose control
- **A dose response is seen with respect to glucose control - with the higher dose providing the most rapid glucose control (purple line)**
- **In contrast, animals with persistent GGG activity showed complete failure in glucose control (dotted line)**

In vivo production of peptide therapeutics addresses several challenges in current pharmacological treatment of metabolic disorders

Short lived agonists in responsive homeostatic systems which function to rapidly react to environmental changes (e.g. food intake) work better when the receptors are not persistently activated



GLP-1 and receptor complex

Efficacy

- Native/natural short acting peptides can be delivered and precisely controlled with oral small molecule inducers
- These may be more efficacious than synthetic injected peptides due to receptor binding dynamics and ability to cross the BBB. Ie: native peptide target the right receptors in the right places
- More efficacious combinations can be designed and tested in weeks without synthetic peptide chemistry, addressing key shortcomings such as muscle loss and fat re-gain
- *in vivo* delivery of short acting agonist peptides results in significantly improved efficacy compared to the same constitutively active peptides
- Improved weight loss and post prandial glucose control

Safety & Tolerability

- Lower levels of short acting native peptides produced endogenously in response to bespoke oral small molecules may have better efficacy, safety and tolerability than persistently active synthetic injectable peptides or small molecule receptor activators

Patient Access, Manufacturing & COGS

- Patient's cells produce the therapeutic peptides, circumventing costly peptide manufacturing and need for injection

Riboswitch-regulated leptin therapy (riboLeptin) - Summary

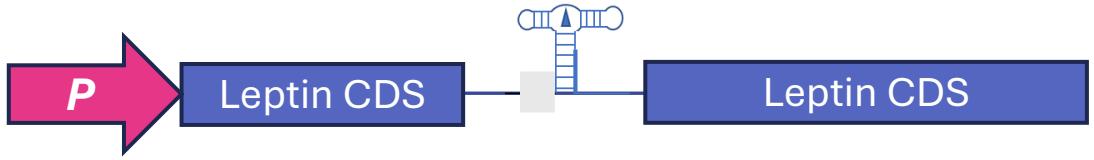
- **Leptin** is a key hormone regulating energy balance and metabolic homeostasis. In healthy individuals, when fat reserves are high, leptin levels rise – signaling satiety and promoting energy expenditure. Conversely, when fat stores are low, leptin levels decrease, triggering hunger and encouraging the body to conserve fat
- **Lipodystrophy:** deficiency or loss of Leptin causes lipodystrophy - a group of potentially life-threatening disorders that affect how the body stores and uses fat. Patients present with a broad range of symptoms, including organ abnormalities (e.g. hepatic steatosis, nephropathy and pancreatitis) and metabolic abnormalities (diabetes, insulin resistance and hypertriglyceridemia)

MeiraGTx is developing a new leptin therapy using its proprietary Riboswitch technology - to deliver native leptin to patients with a daily dose of an oral pill

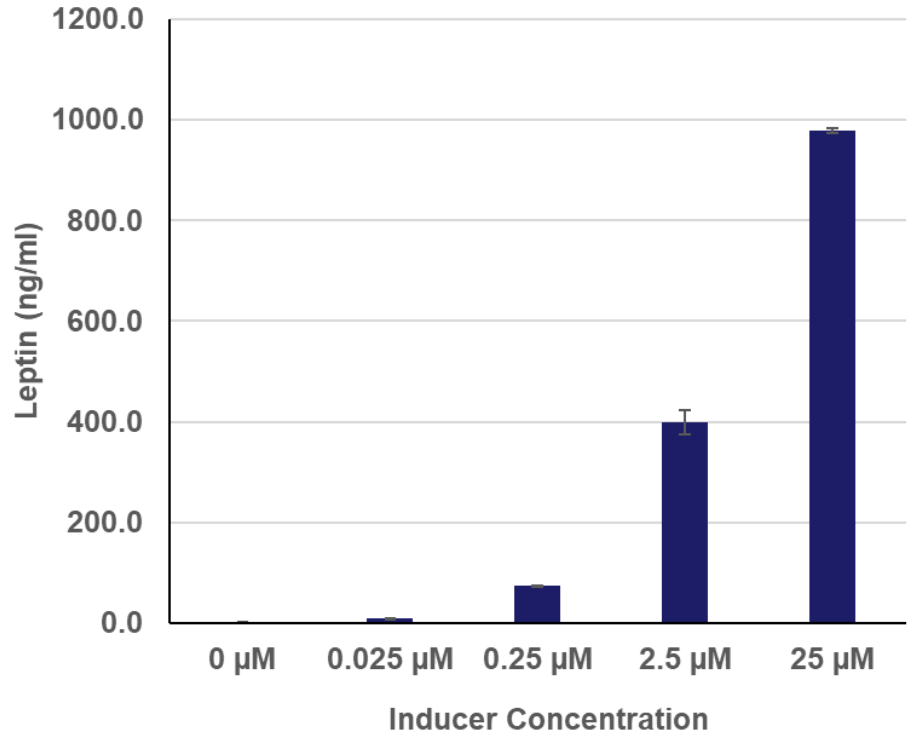
- **riboLeptin offers meaningful potential advantages over current standard of care therapy (metreleptin):**
  - ✓ Reduced risk of immunogenicity (metreleptin carries a black box warning for ADAs)
  - ✓ Avoiding potential toxicity of metreleptin from supraphysiological surges on injection
  - ✓ Physiologically relevant production of native leptin by patient's own cells
  - ✓ riboLeptin is via convenient oral dosing (vs. daily injections)
  - ✓ Lower overall COGS (small molecule vs. recombinant protein production)
  - ✓ Pricing of of injectable metreleptin can be up to $1.3m/year[1]
  - ✓ riboLeptin allows broader access to larger populations at potentially considerably lower cost
- **In a widely accepted *in vivo* model of leptin deficiency (ob/ob mice), riboLeptin treatment led to complete correction of metabolic abnormalities associated with leptin deficiency with daily oral dosing, including:**
  - Dose dependent expression of native human leptin to physiological levels
  - Resolution of excessive food intake (hyperphagia) characteristic of leptin deficiency
  - Significant and durable weight loss - to normal levels
  - Significant reduction in body fat
  - Normalization of triglyceride levels and resolution of liver steatosis
  - Complete restoration of glucose tolerance and normal serum glucose levels

1- https://www.drugs.com/article/top-10-most-expensive-drugs.html

Riboswitch-regulated leptin demonstrates dose-dependent expression *in vitro* in mammalian cells

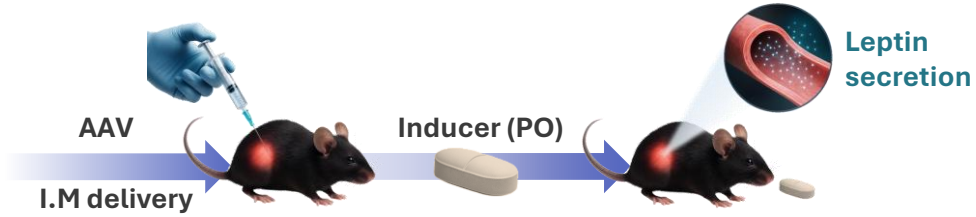


Dose-dependent leptin expression in HEK 293 cells

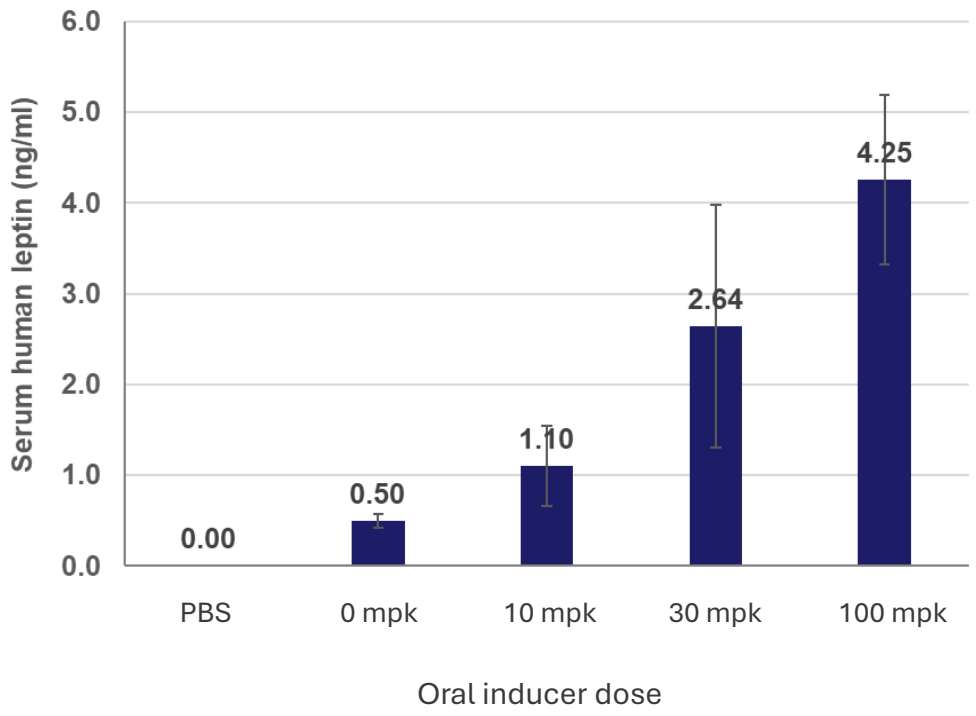


- Riboswitch gene regulation cassette was inserted in the coding sequence (CDS) of human leptin gene
- The construct was transfected into HEK 93 cells
- Transfected cells were treated with riboswitch small molecule inducer MXU-001at the indicated concentrations
- 48 hours after MXU-001 treatment, supernatants were collected and human leptin protein was measured using ELISA assay

Riboswitch-small molecule control of leptin demonstrates dose-dependent expression *in vivo* in leptin deficient ob/ob mice



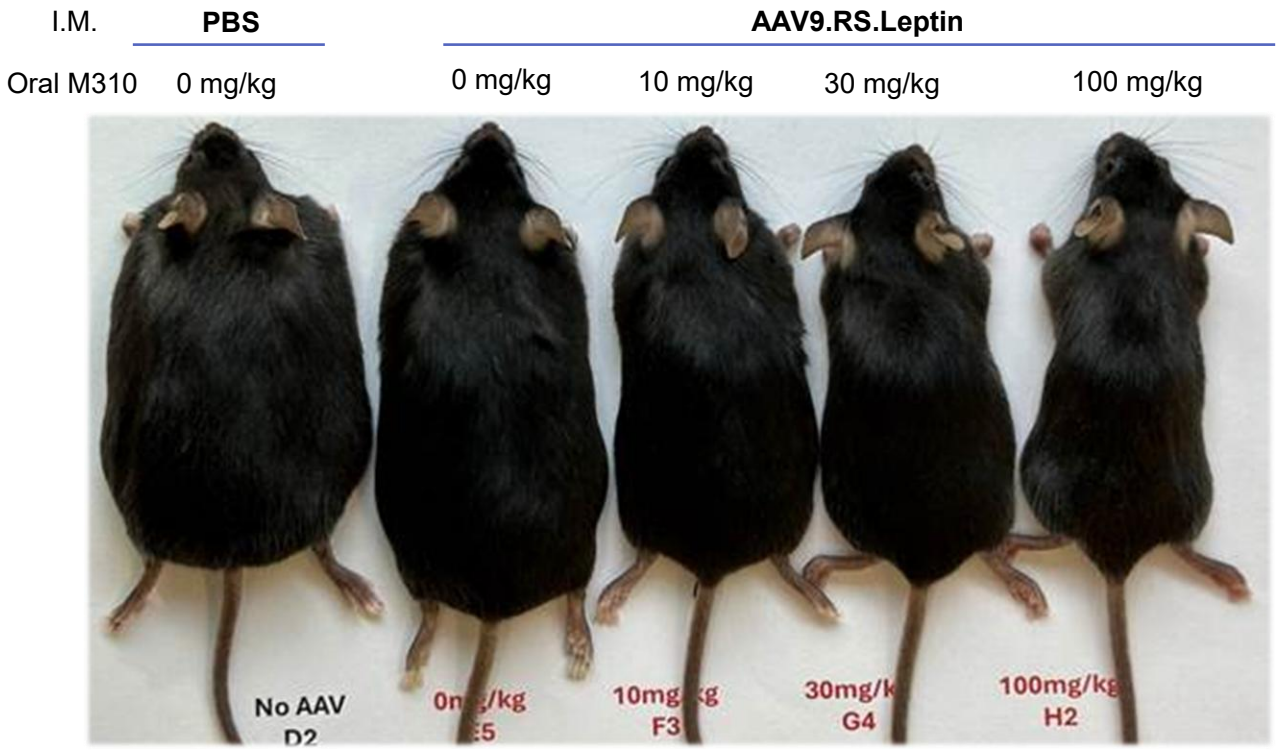
Dose-dependent leptin expression in ob/ob mice



In leptin-deficient mice, leptin is expressed in a dose dependent manner in response to oral dosing with Riboswitch inducer, MXU-001, achieving physiological levels of leptin:

- AAV9 vector containing human leptin gene with Riboswitch cassette (AAV.RS.Leptin) at 1E11 vg/mouse, or PBS as control, was administered as a one-time local injection directly into the leg muscle of ob/ob mice
- 3 days post intramuscular injection, animals were orally dosed with the small molecule inducer M310 at the indicated doses. M310 was given daily for 6 days a week over 5 weeks
- On day 39 post the single IM AAV injection and 16 hours following the last dose of M310, blood samples were collected and the serum levels of circulating human leptin were determined by ELISA specific for human leptin
- Leptin expression levels directly corresponded to the dose of the orally administered inducer M310
- Leptin reached physiological levels in response to 30 mg/kg dose of inducer

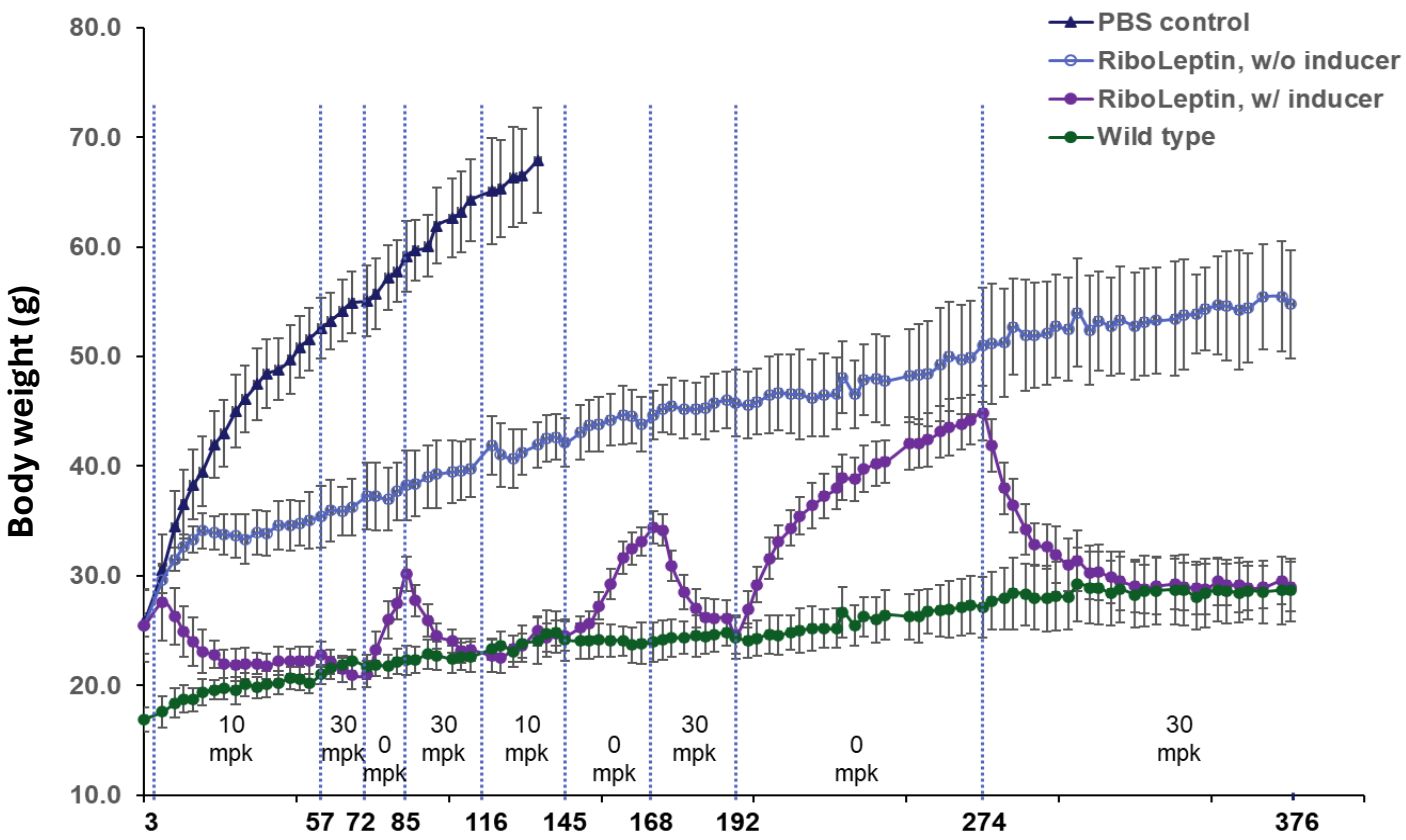
riboLeptin demonstrates dose-dependent weight loss in response to oral inducer dosing, preventing morbid obesity



riboLeptin normalizes body weight and prevents morbid obesity in leptin-deficient mice:

- AAV9 vector containing Riboswitch-controlled human leptin (AAV9.RS.Leptin) at 1E11 vg/mouse or PBS as control was administered as a one-time local injection into the leg muscle of ob/ob mice
- 3 days post intramuscular injection, animals were orally administered the small molecule inducer M310 at 0, 10, 30 or 100 mg/kg doses
- The oral dose of M310 was given daily for 6 days a week over 5 weeks
- On day 33 post the single IM AAV injection, photos of representative mice from each treatment group were taken, demonstrating the therapeutic effect of riboLeptin in normalizing body weight and preventing morbid obesity in leptin-deficient mice

Durable riboswitch-controlled production of leptin in ob/ob mice effectively treats leptin deficiency with daily oral small molecule dosing over a year after one-time IM injection of RiboLeptin



Intervals of daily dosing of oral small molecule inducer

- 5.5 weeks old ob/ob mice were injected with PBS or 1E11 vg AAV9.RS.Leptin (RiboLeptin) into the muscle on Day 1
- 3 days post the single AAV injection, mice were treated with the indicated oral doses of small molecule inducer, daily (10mpk or 30mpk or no small molecule inducer) for consecutive days
- Daily morning dosing of the oral small molecule inducer resulted in rapid reduction in body weight in ob/ob mice to the weight of wild type mice
- When the small molecule was withheld, mice gained weight in the absence of production of effective leptin levels
- Repeated intervals of daily dosing with the small molecule inducer over a period of a year resulted in the same dynamics of leptin production and weight loss on reintroduction of the oral small molecule dosing, **showing long term durability of the riboswitch system**
- Wild type weight is currently being maintained in ob/ob mice with daily oral inducer dosing out past one year following the one-time injection of the Ribo-Leptin DNA template to the muscle

Riboswitch-regulated leptin therapy (RiboLeptin) - Summary

RiboLeptin resolved leptin deficiency following oral inducer treatment in ob/ob mice:

- Dose dependent expression of leptin to physiological levels
- Significant reduction in excessive food intake behavior (hyperphagia)
- Significant and durable weight loss - to normal levels
- Complete correction of body fat levels to normal levels
- Complete correction of glucose tolerance and serum glucose levels
- One-time local injection of gene vector followed by daily dose of oral small molecule
- Much decreased cost of goods, increasing the accessibility of leptin replacement, while replacing injection with a daily oral pill, and reducing toxicity and increasing safety

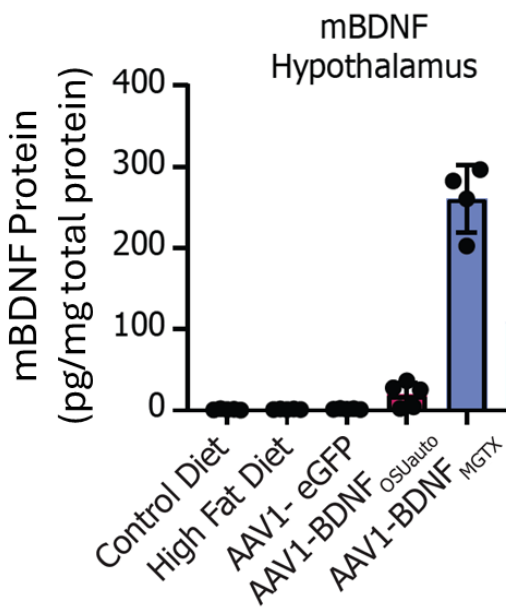
MEIRAGTx

AAV-BDNF: small dose, locally delivered to hypothalamus to change dysregulated MC4R circuitry in the brain

IND Enabling: clear evidence of strong efficacy in animal models

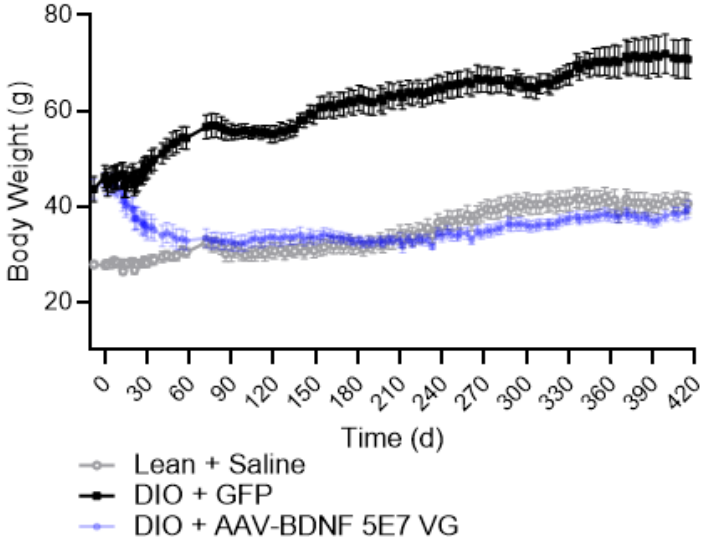
Treatment with AAV-BDNF leads to significant weight loss in obese mice, without muscle loss. Works downstream of MC4R to control weight.

Optimized, high expressing vector



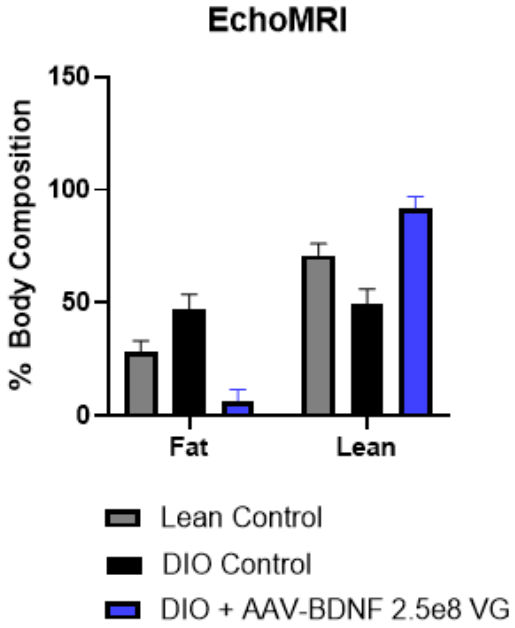
- Vector optimization by MeiraGTx's Vectorology group results in high expression of BDNF in mouse hypothalamus vs. unoptimized vector ("OSUauto"), allowing administration of ultralow vector dose to achieve therapeutic levels of BDNF

Meaningful and durable weight loss in DIO mice



- A single, ultralow dose of AAV-BDNF to the brain of obese mice causes significant weight loss that is stable throughout their lifespan (>14 months post treatment).

Significant fat reduction without affecting lean muscle mass



- AAV-BDNF treatment leads to significant fat reduction, while maintaining lean muscle composition

MEIRAGTx

Additional information available under CDA

MeiraGTx is leading the next wave of genetic medicines

Advanced and diverse pipeline of genetic medicines

- **4 pivotal stage programs:** Radiation-induced xerostomia, Parkinson's disease, AIPL1 retinal dystrophy, X-linked retinitis pigmentosa
- **Diverse preclinical pipeline:** ALS, intractable neuropathic pain, obesity & diabetes, large ophthalmology indications such as Stargardt's, wet AMD and dry AMD
- **Multiple potential near-term BLA filings**

Powered by best-in-class genetic medicine technologies and unique industry leading end-to-end in-house GMP manufacturing:

Vector Design & Optimization Technologies

- ☑ Novel intravitreal capsids
- ☑ Proprietary promoters
- ☑ Sequence optimization
- ☑ Proprietary non-coding elements for increased potency

Riboswitch Platform

- ☑ Precise control of transgene expression with orally administered pills
- ☑ New approach to cell therapy, gene editing, metabolic disease

End-to-end GMP Manufacturing

- ☑ In-house viral vector GMP manufacturing
- ☑ Commercially-licensed QC facility
- ☑ Fill & Finish
- ☑ Single use – flexible & scalable production

MEIRAGTx