QurAlis™

Driving scientific breakthroughs into powerful precision medicines for ALS and other neurodegenerative diseases

January 2025

Driving scientific breakthroughs into powerful precision medicines

Groundbreaking science

Next-gen precision medicines developed by **human disease models** pioneered by QurAlis founders

Targeting **RNA restoration** in validated genetic disease resulting from mis-splicing targets in neurodegeneration and beyond

Utilizing **biomarkers** for patient selection, target engagement, and efficacy

First & best-in-class programs

Multiple assets in the clinic with disease-relevant biomarker readouts in 2025

Three first-in-class programs **on novel genetic targets** for sporadic ALS

Proprietary FlexASO® platform to enable additional RNA restoration therapies

World-class team to execute

Experienced executive team

UNC13A partnership with Lilly highlights value of FlexASO® platform

$143.5M equity raised, in addition to Lilly partnership upfront

QurAlis' diversified pipeline across CNS disorders

Program	Disease mechanism	Modality	MOA	Indication	Preclinical	Clinical	Partner
QRL – 101	Splicing	Small molecule	Kv7.2/3	ALS			
				Epilepsy			
QRL – 201	Splicing	ASO	STMN2	ALS			
QRL – 203				FTD (non-Tau)			
QRL – 204	Splicing	ASO	UNC13A	ALS / FTD			Lilly
Discovery programs							
QRL – TBA	Splicing	ASO	Undisclosed				
QRL – TBA							

- Ion Channel Recovery platform expansion beyond ALS to other indications creating additional growth opportunities
- Disease-modifying first-in-class RNA restoration programs for four high profile rare diseases with genetic splicing targets
- QurAlis' FlexASO® platform provides unique opportunities for expansion into further RNA restoration targets

QurAlis' expertise and technologies enable two distinct franchises

Pursuing treatment for CNS disorders with innovative biology and proven modalities

Ion Channel Recovery

- Neurological disorders often result from ion channel dysfunction
- Kv7.2/7.3 potassium channel is a drug target for >10 high unmet need indications, multiple indications with clinical validation, including:
  - >50% of ALS
  - Epilepsy
  - Pain
  - Mood disorders
- Highly selective Kv7.2/7.3 opener well positioned as potential best-in-class therapeutic:
  - High selectivity, lack of off-target engagement controls AE rates
  - Formulations optimized for different indications

RNA Restoration

- Potential to develop first-in-class and best-in-class medicines through FlexASO® platform
  - Active antisense oligonucleotide (ASO) candidates in Phase 1 (1x) and FIH-enabling studies (2x)
- Specifically addresses mis-splicing targets which underly biology of neurodegenerative diseases including:
  - TDP-43-opathies
  - Tau-opathies
  - Fragile X syndrome
- Multiple candidates generated to date with reproduceable path to IND and Proof of Concept (PoC)
  - Includes QRL-204 (UNC13A) program licensed to Eli Lilly

Pioneers with unrelenting commitment to patients

Kasper Roet, PhD
CEO
Co-founder

HARVARD MEDICAL SCHOOL
Johnson & Johnson

Dan Elbaum, PhD
CSO

Retrophin
Pfizer
AMGEN
CRITICAL Therapeutics
FoldRx
VERTEX
Ra Pharma

Vikas Sharma, PhD
CBO

bioxcel therapeutics
MACROGENICS
AstraZeneca
MedImmune
rexahn PHARMACEUTICALS

Hagen Cramer, PhD
CTO

Avecia
Girindus Solvay Organics
Ridgeway Biosystems Inc.
WAVE LIFE SCIENCES

Robin Wojcieszek, PharmD
Head of Regulatory Affairs & Drug Safety

Lilly
FibroGen
Pfizer
Lundbeck
FDA

Doug Williamson, MD
CMO

Lilly
parexel
Lundbeck

Emma Bowden, PhD
Head of Development

Lilly
Sangamo THERAPEUTICS
ThermoFisher SCIENTIFIC
AstraZeneca
MedImmune

Jason Brown, MBA
CFO

KARUNA THERAPEUTICS
PURETECH GIVING LIFE TO SCIENCE
NOVARTIS

Advised by leading clinicians and scientists in neurodegeneration field

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Matthew Kiernan
MD, PhD
The University of Sydney
The University of Sydney Brain and Mind Centre


Bernhardt Trout
PhD
MIT Massachusetts Institute of Technology


Brian Wainger
MD, PhD
Harvard Medical School
Massachusetts General Hospital


Christopher Shaw
MD, PhD
King's College London


Sudhir Agrawal
PhD
idera
University of Massachusetts Amherst


Michelle Hastings
PhD
University of Michigan

Supported and recognized by investors, pharma, and industry

Investors

EQT Life Sciences
sanofi ventures
DROIA ventures
Lilly
LS POLARIS INNOVATION FUND
AMGEN
mission BIOCAPITAL
Dementia Discovery Fund
inkef capital
ALS INVESTMENT FUND
DOLBY FAMILY VENTURES
MP Healthcare Venture Management, Inc. Mitsubishi Tanabe Pharma Group
MITSUI GLOBAL INVESTMENT
Mass General Brigham Ventures
ALEXANDRIA.

Awards

FIERCE Biotech FIERCE 15 2020 WINNER
NEVY 2020 AWARDS presented by DELL Technologies WINNER
THE TERMEER FOUNDATION

Collaborators

Lilly
QRL-101 in-license
QRL-204 out-license

UMass Chan MEDICAL SCHOOL
Fragile X

Ion Channel Recovery

Ion channel dysfunction is implicated across wide range of CNS disorders

Kv7.2/3 channel openers have biological validation across variety of disease models

- GSK's ezogabine was studied in multiple indications including pain, seizure, and mood disorders and marketed for partial-onset seizures before being withdrawn (2017) for undesirable side effect profile, limiting commercial potential
  - Ezogabine also demonstrated signal of disease modification in PoM trial in ALS[1], where hyperexcitability is a key characteristic in up to 40-70% of ALS patients
- Further validation of Kv7.2/3 has been demonstrated by XEN1011 and other clinical programs in epilepsy studies

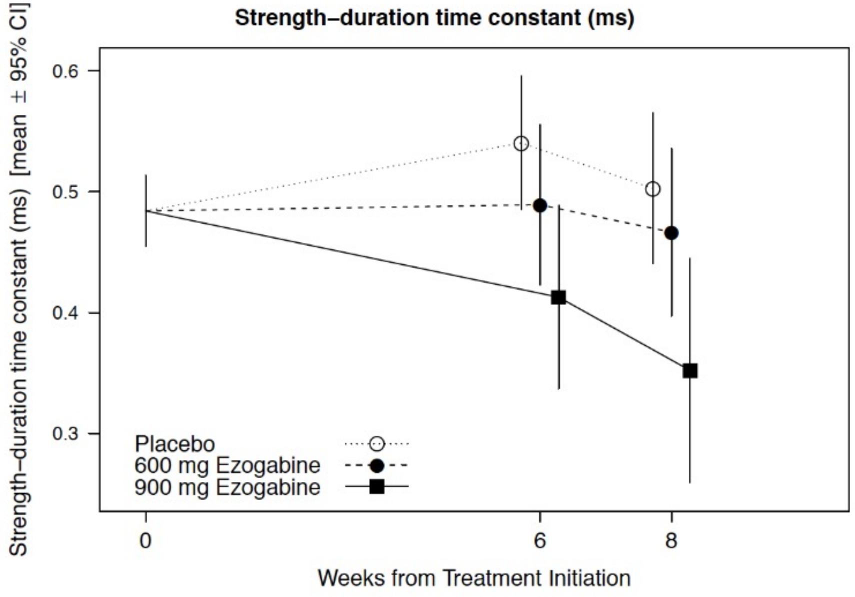
- QurAlis is developing QRL-101, a highly selective Kv7.2/3 channel opener for ALS and epilepsy with ongoing PoM studies to inform dosing & indication selection for Phase 2
  - High affinity to Kv7.2/3
  - Lack of affinity for GABA-A receptors and other Kv7 subtypes

Wainger BJ, Macklin EA, Vucic S, et al. *JAMA Neurol.* 2021;78(2):186–196. doi:10.1001/jamaneurol.2020.4300

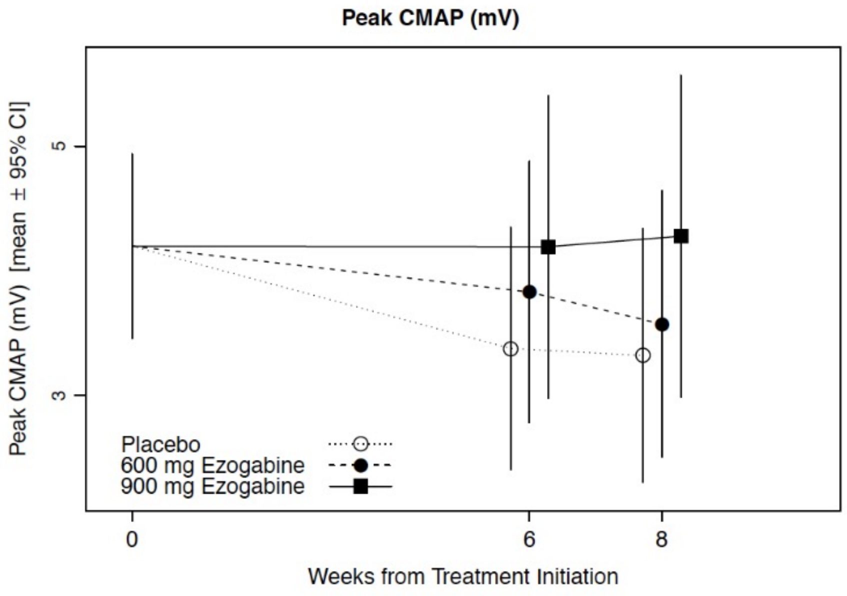
Kv7 is a clinically validated target in ALS

Ezogabine published trial results (n= 65 patients) validated the importance of reducing hyperexcitability through Kv7

Significant dose-dependent effects on biomarkers that predict patient survival



Significant correlation between effect sizes of excitability biomarker (SDTC) and efficacy biomarker (CMAP)

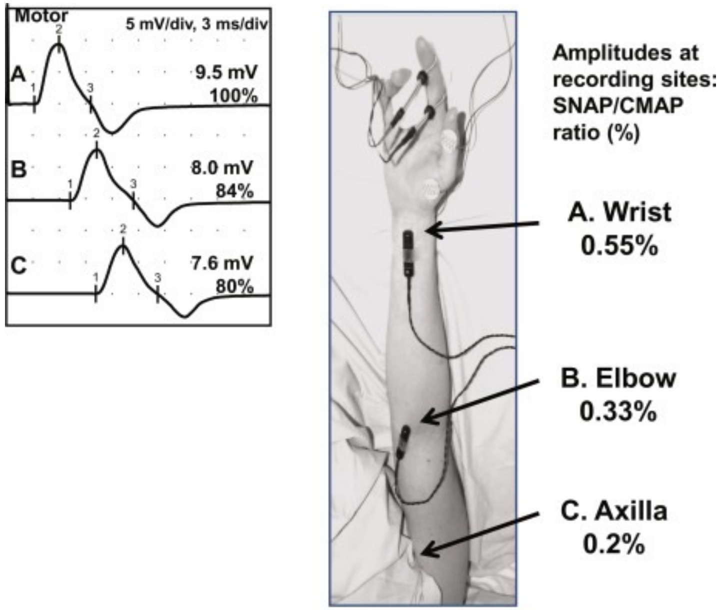


Nearly all (97%) participants in the trial reported at least one adverse event
Most frequent adverse events among participants in the ezogabine arms were fatigue and dizziness

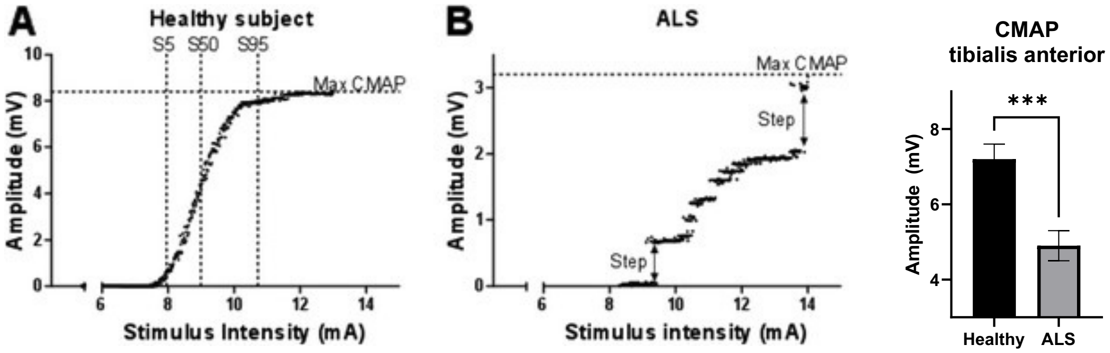
Wainger BJ, Macklin EA, Vucic S, et al. *JAMA Neurol.* 2021;78(2):186–196. doi:10.1001/jamaneurol.2020.4300

CMAP is a powerful disease progression and efficacy biomarker that measures muscle innervation in ALS

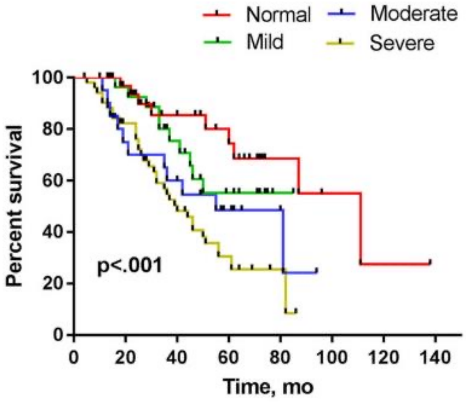
CMAP amplitude measures signal strength from nerve to muscle: number of innervating fibers



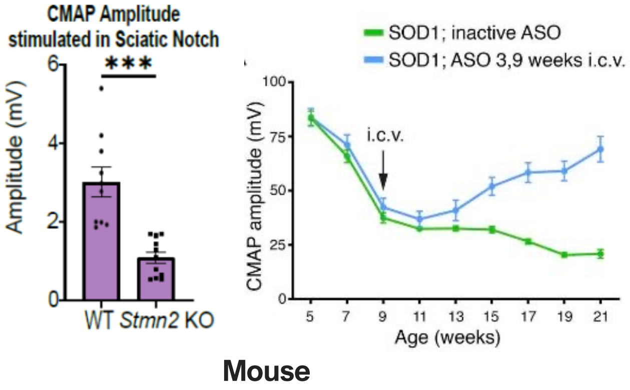
CMAP is used to monitor disease progression in ALS patients



CMAP amplitude predicts survival in ALS



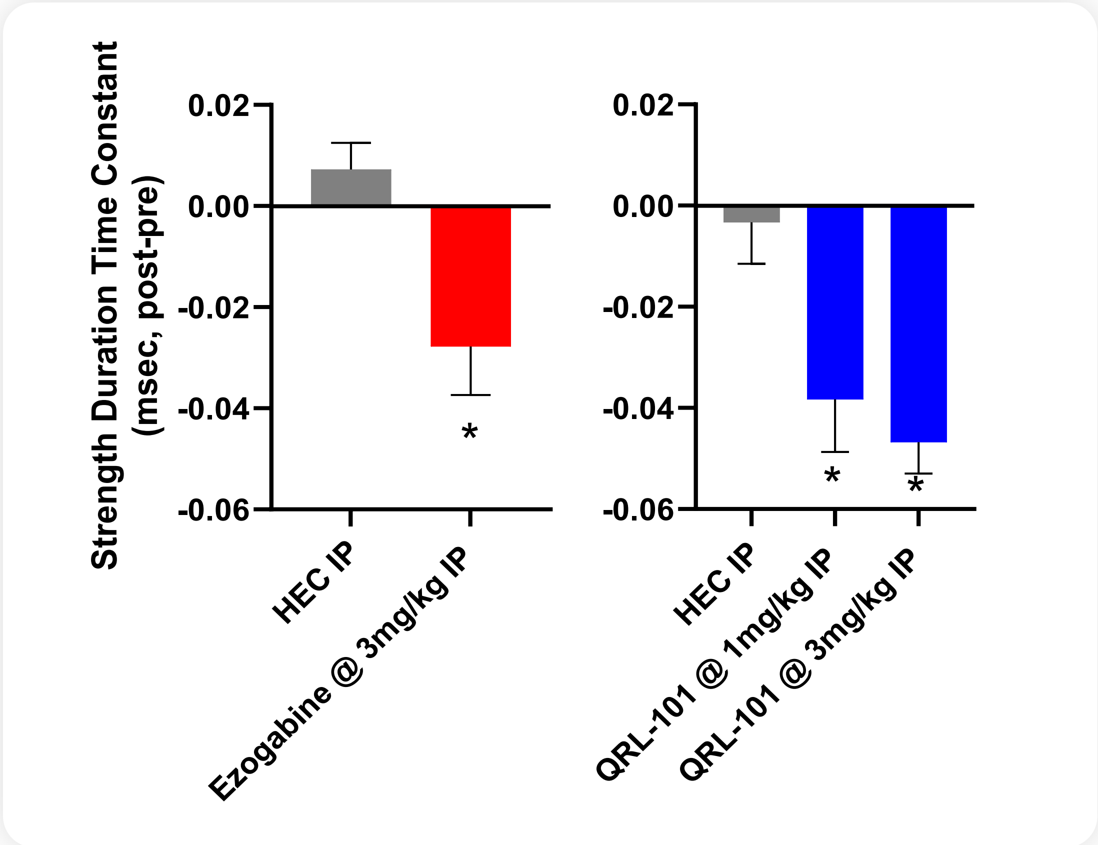
CMAP amplitude can show therapeutic effect of ASO

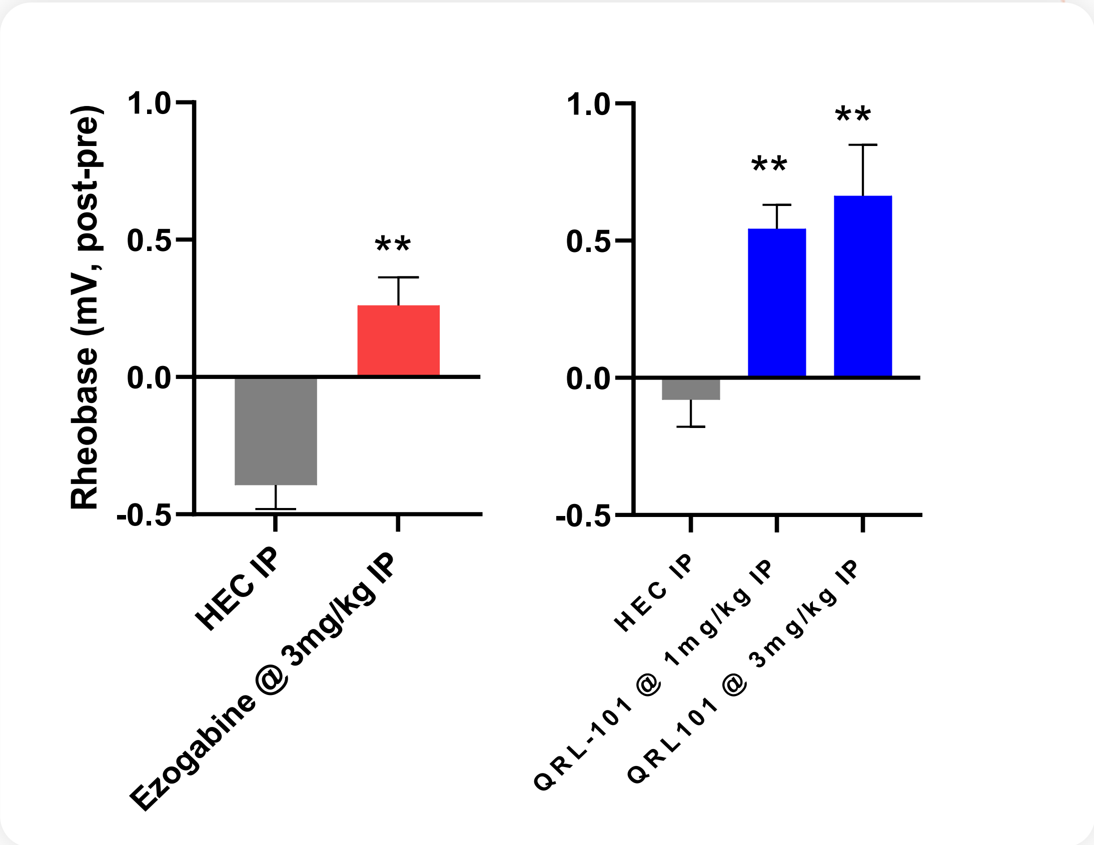


1. Clarissa Crone, Christian Krarup, in *Handbook of Clinical Neurology*, 2013
2. Maathuis et al., 2013 *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2013; 14: 217–223
3. Yu et al., 2021 *Front Neurol*. 2021 Feb 11;12:574919. doi: 10.3389/fneur.2021.574919
4. McCampbell et al., 2018 *J Clin Invest*. 2018;128(8):3558-3567. https://doi.org/10.1172/JCI99081.
5. Krus et al., 2022 *Cell Rep* Jun 28;39(13):111001. doi: 10.1016/j.celrep.2022.111001

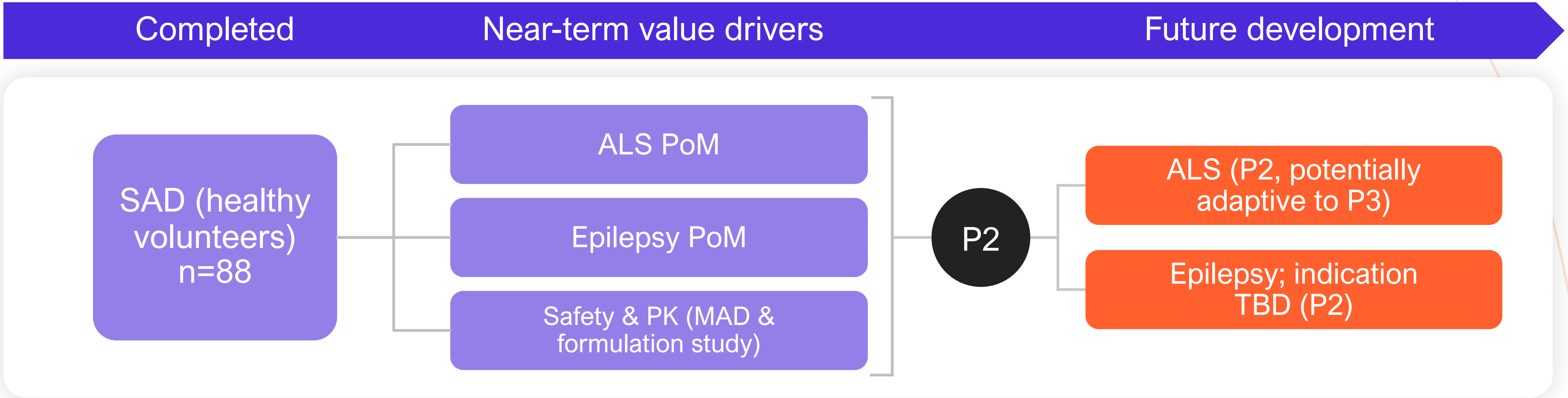
QRL-101 shows superior *in vivo* potency in ALS disease model compared to ezogabine

- Statistically significant effect on both Strength Duration Time Constant (SDTC) and Rheobase at 1 and 3 mg/kg in rats
- Effects are larger than the ezogabine effects at 3 mg/kg
- At both 1 and 3 mg/kg QRL-101 exceeded 15% decrease in SDTC, which corresponds to ezogabine clinical effect size





PoM studies for ALS and epilepsy to support dose selection for PoC trials



Key findings

- Generally well tolerated, large majority of AEs were mild in nature
- No treatment-emergent SAEs reported

Key outcomes

- Biomarker validation across multiple disease models
- Doses & improved formulation(s) for PoC studies

MAD: Multiple Ascending Dose; PoM: Proof of Mechanism; PoC: Proof of Concept; PK/FE: Pharmacokinetics / Food Effect

PoM studies include broad range of disease-relevant electrophysiological and target engagement biomarkers

ALS PoM Design

- Single-dose placebo-controlled design at three ascending dose levels
- 12 patients (four per dose level)
- Safety and tolerability in ALS patients
- PK/PD assessment at each dose level

Disease-relevant biomarkers collected

- Endpoints associated with peripheral nerve excitability threshold tracking
- Includes strength-duration, recovery cycle, threshold electrotonus and current / voltage; all output measures shown to be disrupted in ALS
- ALS biomarkers also included in epilepsy PoM to supplement dataset

Epilepsy PoM Design

- 24 healthy volunteers
- Three-way crossover design (placebo, low dose, high dose)
- PD/PK assessments in each treatment period

Disease-relevant biomarkers collected

- Endpoints associated with central nerve excitability and electrical activity in the brain
- Transcranial magnetic stimulation (TMS) endpoints; motor evoked potential (MEP); resting motor threshold (RMT), peak to peak amplitude
- Pharmaco-electroencephalography (pEEG) endpoints; changes in passive EEG

Topline data for both studies are expected H1 2025

RNA Restoration: STMN-2 Programs

STMN2-targeting ASO leads RNA restoration franchise

STMN2 is the most consistently downregulated gene in sporadic ALS patients

- Restoration of STMN2 pre-mRNA mis-splicing through ASO treatment restores neuronal processes, Golgi outposts, and protects neuronal activity in human motor neurons with TDP-43 pathology
- Genetic target in sporadic ALS (90% of patients) and FTD (50% of patients) as well as Alzheimer's Disease (~33% of patients)
- Two approved ASO therapies for motor neuron diseases (Spinraza® for SMA and Qalsody® for ALS) demonstrate that an ASO therapy strategy to restore STMN2 in ALS patients is technologically feasible

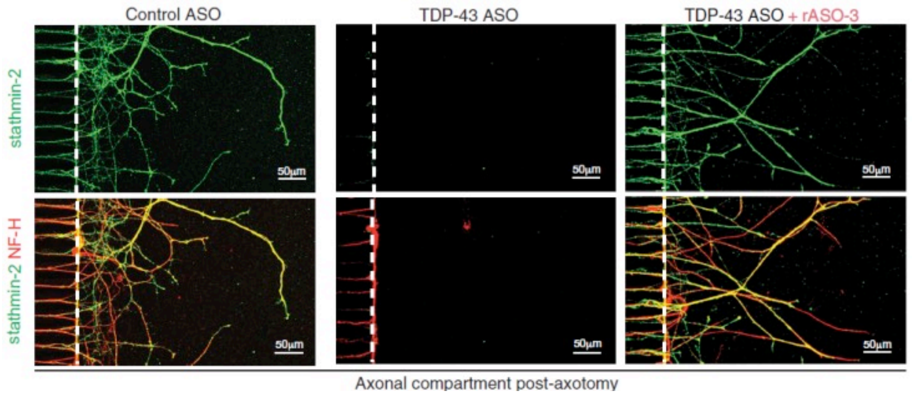
- QurAlis is developing QRL-201, a highly potent splice-switching ASO targeting STMN2
- MAD study (ANQUR) expanded to dose range-finding portion (at two dose levels) and ongoing with favorable safety and tolerability profile to date
- Multiple biomarkers under assessment to support future development strategy
- QurAlis retains full global rights; CoM patent through 2039 plus potential PTE, pending issuance

Restoration of STMN2 levels by ASO is a promising therapeutic strategy for the majority of ALS patients

QRL-201 restores full length STMN2

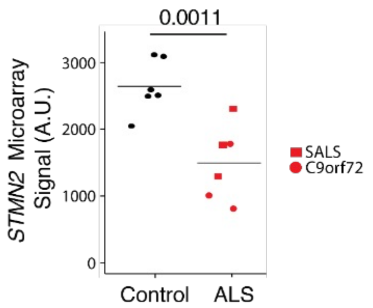
Breakthrough discovery shows TDP-43 driven neurodegenerative phenotypes caused by STMN2 loss

Loss of TDP-43 from the nucleus (ALS hallmark) leads to loss of STMN2	TDP-43 loss causes loss of axons; rescue by restoring STMN2 levels

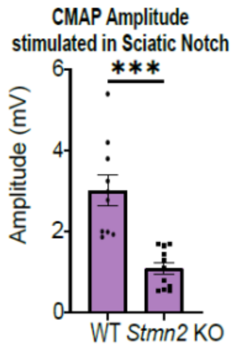


STMN2 is downregulated in ALS patients

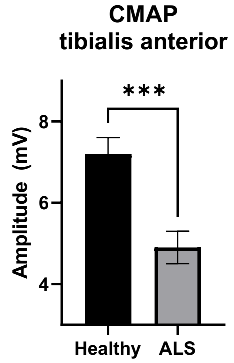
Highley et al 2014 Microarray Laser Capture Motor neuron



Loss of STMN2 leads to denervation of muscles as measured by CMAP Amplitude

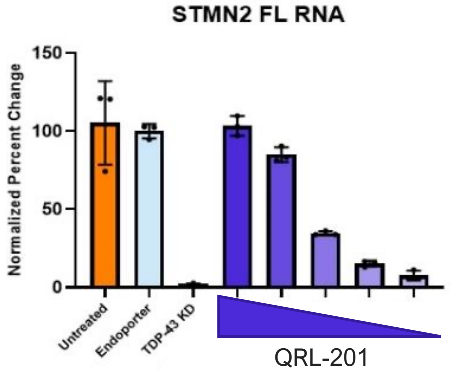


Mouse

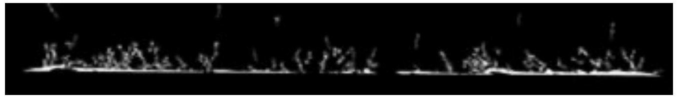


Human

QRL-201 restores STMN2



QRL-201 restores neuronal processes



TDP-43 Pathology

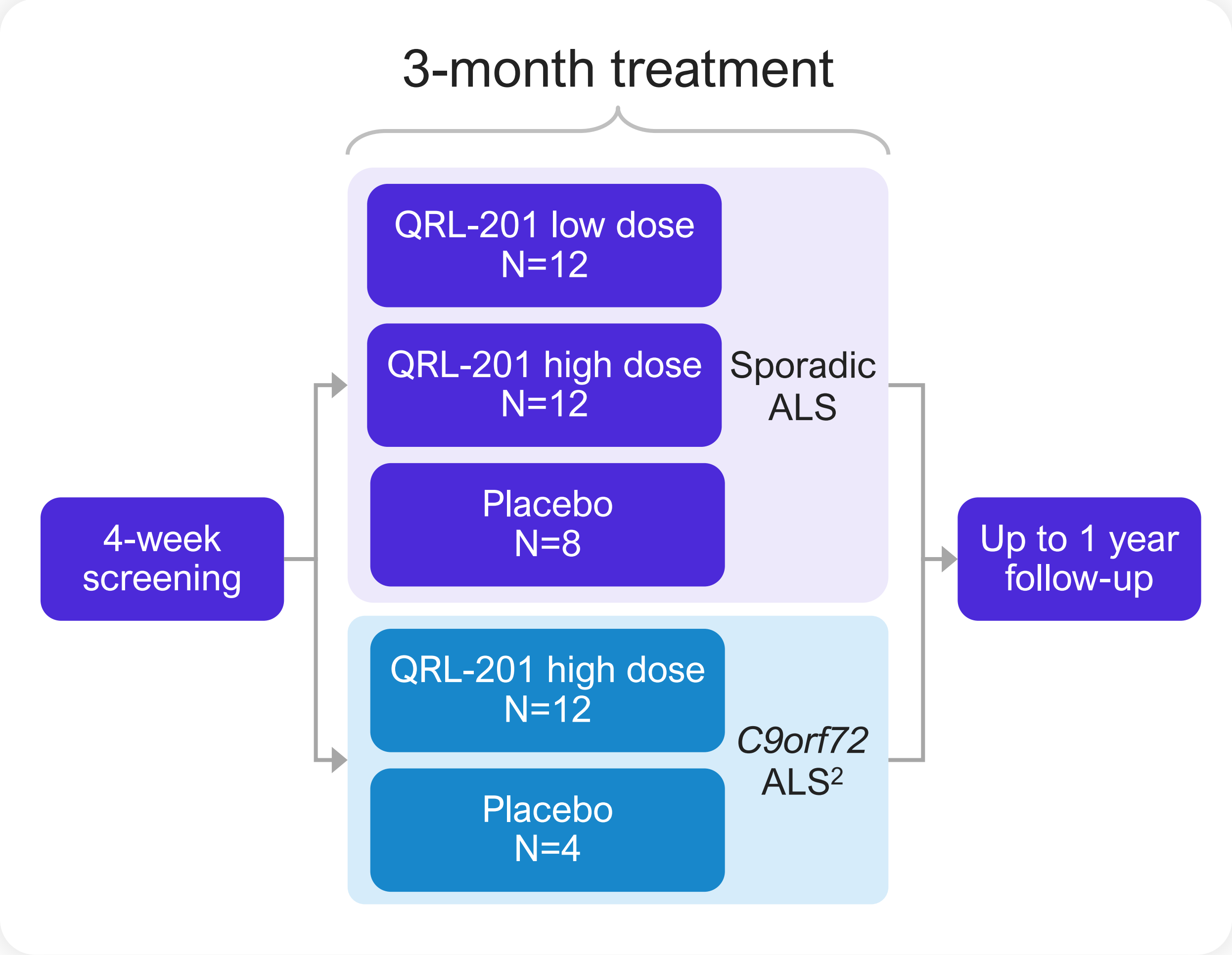
TDP-43 Pathology +QRL-201 (STMN2 Rescue)

1. Melamed Z, López-Erauskin J, Baughn MW, et al. Premature polyadenylation-mediated loss of stathmin-2 is a hallmark of TDP-43-dependent neurodegeneration. *Nat Neurosci.* 2019;22(2):180-190. doi:10.1038/s41593-018-0293-z
2. Klim, J.R., Williams, L.A., Limone, F. et al. ALS-implicated protein TDP-43 sustains levels of STMN2, a mediator of motor neuron growth and repair. *Nat Neurosci* 22, 167–179 (2019). https://doi.org/10.1038/s41593-018-0300-4
3. Baughn, M. W., et al. (2023). "Mechanism of STMN2 cryptic splice-polyadenylation and its correction for TDP-43 proteinopathies." *Science* 379(6637): 1140-1149.
4. Krus et al., 2022 *Cell Rep* Jun 28;39(13):111001. doi: 10.1016/j.celrep.2022.111001

AnQur

ANQUR study progressed to dose range-finding phase, focused on signal detection and safety

Enrollment initiated, seven-month interim data[1] expected H1 2026



Design	Randomized, double-blind, placebo-controlled
Population	32 sporadic ALS patients 16 *C9orf72* ALS patients
Key entry criteria	Symptom onset within 24 months of screening Slow vital capacity >50% Clinical evidence of low motor neuron involvement Stable dose of current treatment during study
Endpoints	1º: Safety & tolerability 2º: Efficacy & biomarker panel

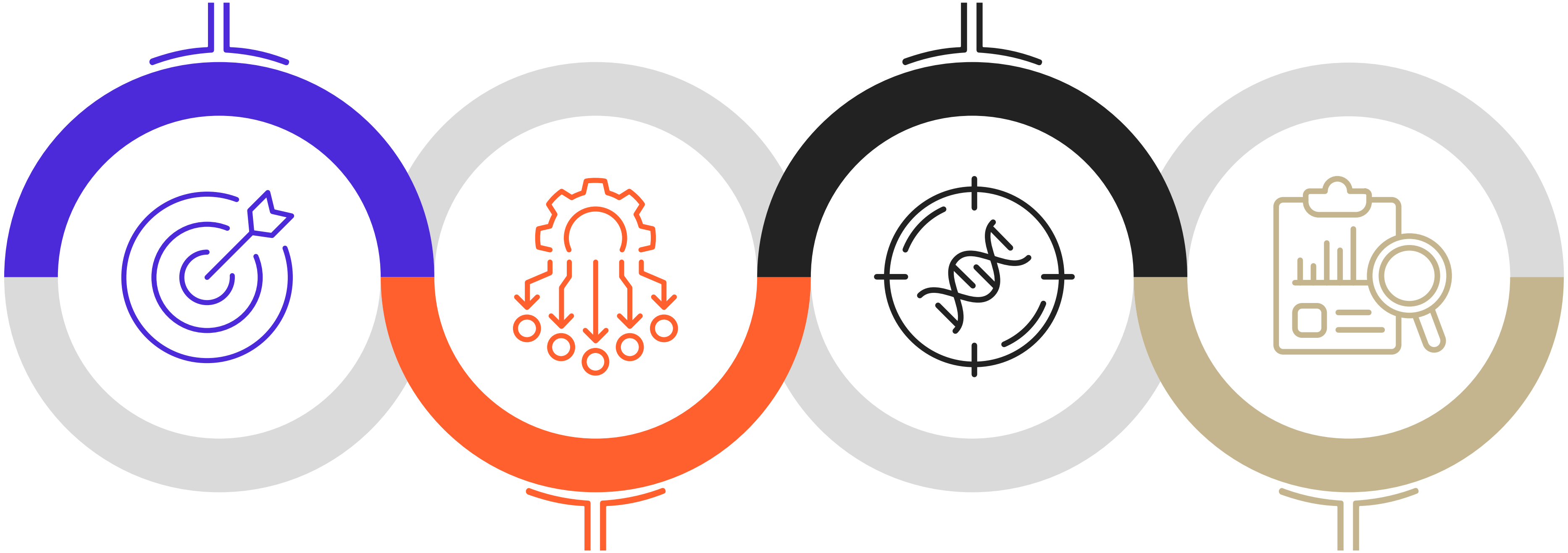
[1] 3-months dosing and 4-months post-dosing follow-up
[2] C9orf72 patients are a homogenous population with consistently decreased STMN2 levels

AnQur

Combination of clinical readouts and extensive biomarker analysis to inform optimal registrational studies

Target engagement
- STMN2 levels

Biomarkers of neuronal loss
- NfL and other exploratory biomarkers



Mechanism of action (MOA)
- Motor excitability recordings (CMAP, M-Scan)
- Established NMJ innervation measurements (STMN2 MOA / efficacy)

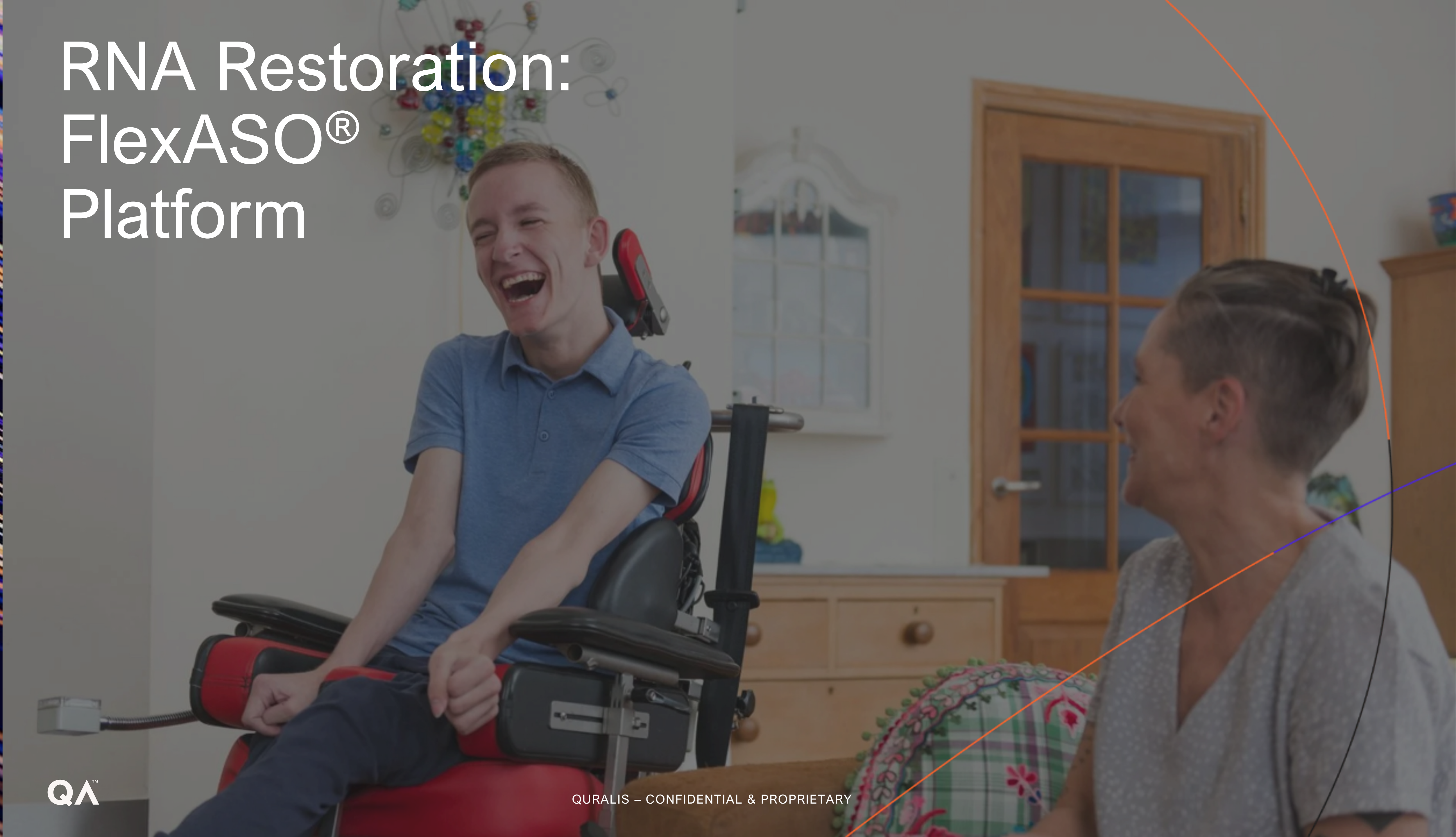
Clinical measurements
- ALSFRS-R, ROADS, SVC, HHD
- Ventilation assistance-free survival
- Time-to-event measures

QRL-201 key take-aways

- STMN2 is the most consistently observed mis-spliced protein in sporadic ALS leading to loss of function
- Downregulation and loss of STMN2 alone in mice leads to loss of muscle innervation, motor neuron axonopathy and muscle atrophy, all hallmarks of ALS
- QRL-201 restores STMN2 levels in human ALS motor neurons
- Preliminary cohorts in the ANQUR study demonstrate that QRL-201 can be well tolerated in ALS patients at exposures far above the predicted minimally efficacious exposure
- A dose range-finding study for QRL-201 is currently active in six countries with biomarkers that can measure efficacy in ALS patients

ANQUR study seven-month efficacy marker & safety data expected H1 2026
Next Ph2 / Ph3 study is a potential registrational study

RNA Restoration: FlexASO® Platform



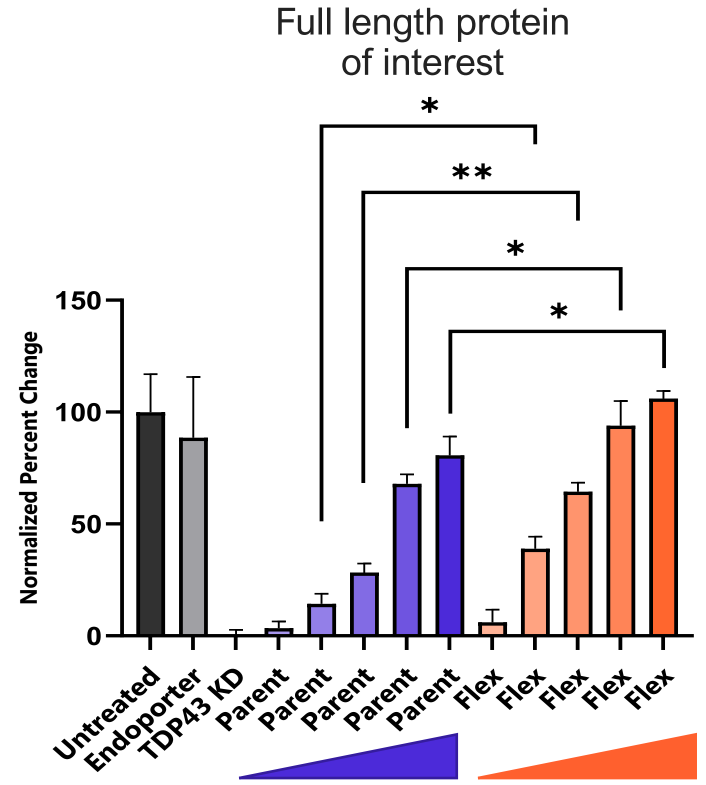
Flex ASO® is the leading splice-modulation platform to restore RNA

FlexASO® is a proprietary ASO splice-modulator platform that incorporates a unique backbone, providing advantages over traditional ASOs

Attributes	Flex ASO	Traditional ASO
Size	✓	✓
Efficacy	✓✓	✓
Safety	✓✓	✓
CMC	✓	✓
Distribution	✓✓	Known for spinal cord and frontal cortex

Potential to overcome modality-specific, dose-limiting toxicities

FlexASO® demonstrates statistically significant increase in RNA restoration vs. parent



Genetic understanding of diseases and tech breakthroughs generate opportunity to develop RNA restoration therapies

Technological breakthroughs

- Technology to cross blood-brain-barrier has matured (e.g., Transferrin receptor)
- Technology to potentially support 2x / year dosing has been developed (e.g., FlexASO® tech.)
- Patient-derived human disease models increase probability of success

Disease-modifying RNA therapies

RNA restoration oligonucleotides targets

- Diseases caused by haploinsufficiency (e.g., Dravet)
- Diseases caused by mis-splicing (e.g., SMA, ALS, FTD, Fragile X, PSP)
- Previously undruggable targets for large indications

Driving scientific breakthroughs into powerful precision medicines

Groundbreaking science

Next-gen precision medicines developed by **human disease models** pioneered by QurAlis founders

Targeting **RNA restoration** in validated genetic disease resulting from mis-splicing targets in neurodegeneration and beyond

Utilizing **biomarkers** for patient selection, target engagement, and efficacy

First & best-in-class programs

Multiple assets in the clinic with disease-relevant biomarker readouts in 2025

Three first-in-class programs **on novel genetic targets** for sporadic ALS

Proprietary FlexASO® platform to enable additional RNA restoration therapies

World-class team to execute

Experienced executive team

UNC13A partnership with Lilly highlights value of FlexASO® platform

$143.5M equity raised, in addition to Lilly partnership upfront

QurAlis™

Thank you

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