QurAlis™

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

June 2025

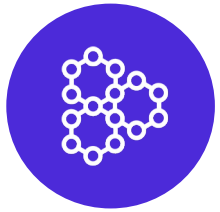
Driving scientific breakthroughs into powerful precision medicines

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

Proprietary FlexASO® platform can potential expand to additional RNA restoration therapies



First & best-in-class programs

Multiple programs in the clinic with near-term data readouts

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

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

World-class team to execute

Experienced executive team

UNC13A partnership with Lilly underscores value of FlexASO® platform

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

Advancing precision neuroscience pipeline across multiple clinical and preclinical programs

Program	MOA	Indication	Upcoming Milestone(s)	Discovery	IND-Enabling	Ph1 Safety / PoM[1]	Proof of Concept	Registration Studies	Partner
QRL-201	STMN2	ALS	ANQUR readout H1 2026						
QRL-101	Excitatory (Kv7)	ALS	Patient PoM[1] study topline Q3 2025						
		Epilepsy / Pain	Proof of Concept initiation H1 2026						
QRL-204	UNC13A	ALS / FTD	IND-enabling studies ongoing[2]						Lilly
QRL-TBA	FMR1	Fragile X	DC[3] 2026						
QRL-TBA	Undis.	PSP	DC 2026						

1. PoM = Proof of Mechanism; 2. In partnership with Lilly; 3. DC = development candidate nomination

QurAlis' expertise and technologies enable two distinct franchises

Pursuing treatment for CNS disorders with innovative biology and proven modalities

Ion Channel Recovery
(small molecule)

- 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
(antisense oligonucleotide ,"ASO")

- 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 (1x)
- 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

Emma Bowden, PhD

Head of Development

Jason Brown, MBA

CFO

Hagen Cramer, PhD

CTO

Dan Elbaum, PhD

CSO

Vikas Sharma, PhD

CBO

Robin Wojcieszek, R.Ph.

Head of Regulatory Affairs & Drug Safety

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 Dell Technologies WINNER
The Termeer Foundation

Collaborators

Lilly
QRL-101 in-license
QRL-204 out-license
UMass Chan Medical School
Fragile X

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

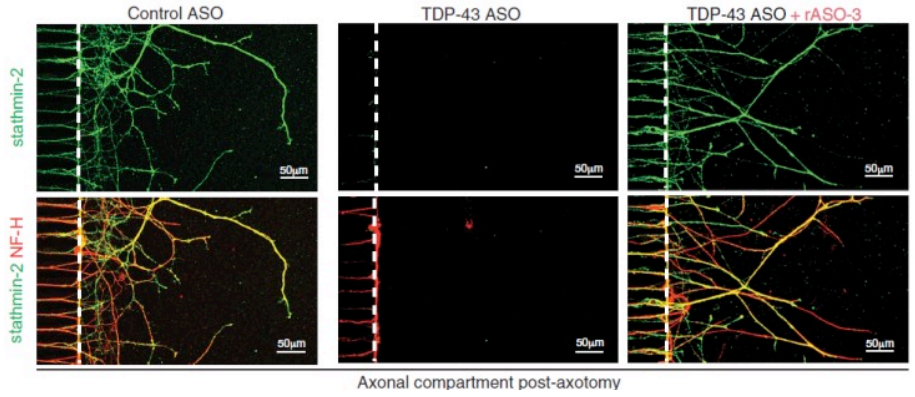
Restoration of STMN2 levels by ASO is a promising therapeutic strategy for the majority of ALS patients

QRL-201 restores full-length STMN2 and protects neurons from degeneration phenotypes

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

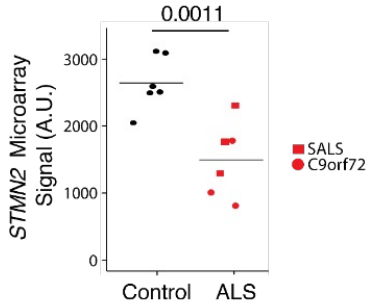
Loss of TDP-43 from the nucleus (ALS hallmark) leads to loss of STMN2

TDP-43 loss causes loss of axons; rescue by restoring STMN2 levels

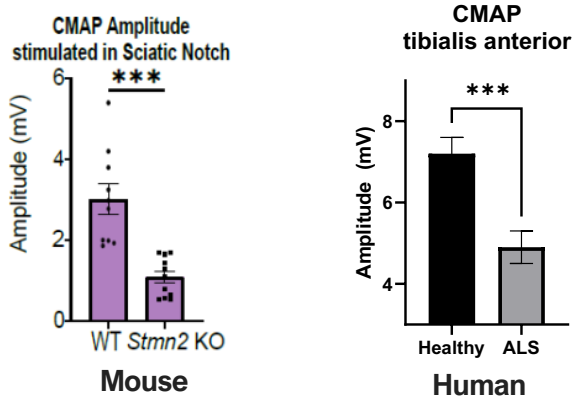


STMN2 is downregulated in ALS patients

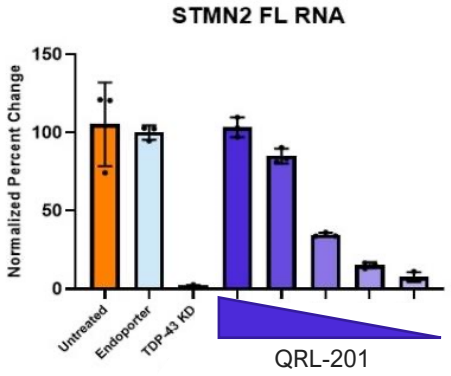
Highley et al 2014 Microarray Laser Capture Motor neuron



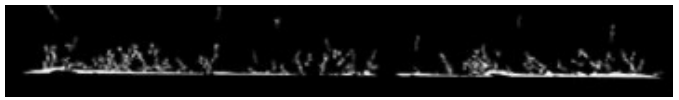
Loss of STMN2 leads to denervation of muscles as measured by CMAP Amplitude



QRL-201 restores STMN2



QRL-201 restores neuronal processes



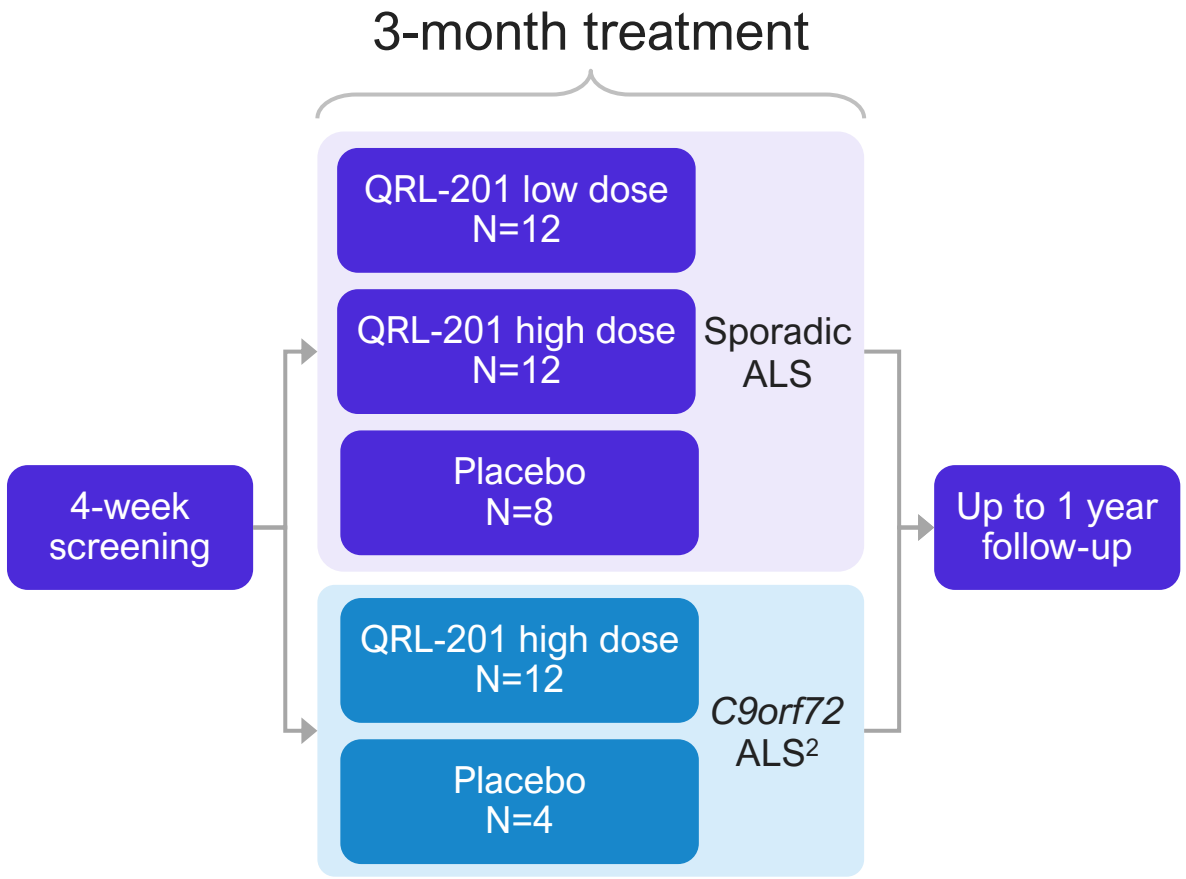
TDP-43 Pathology

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

Enrollment initiated, 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] Exact interim data cut to be finalized
[2] C9orf72 patients are a homogenous population with consistently decreased STMN2 levels

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

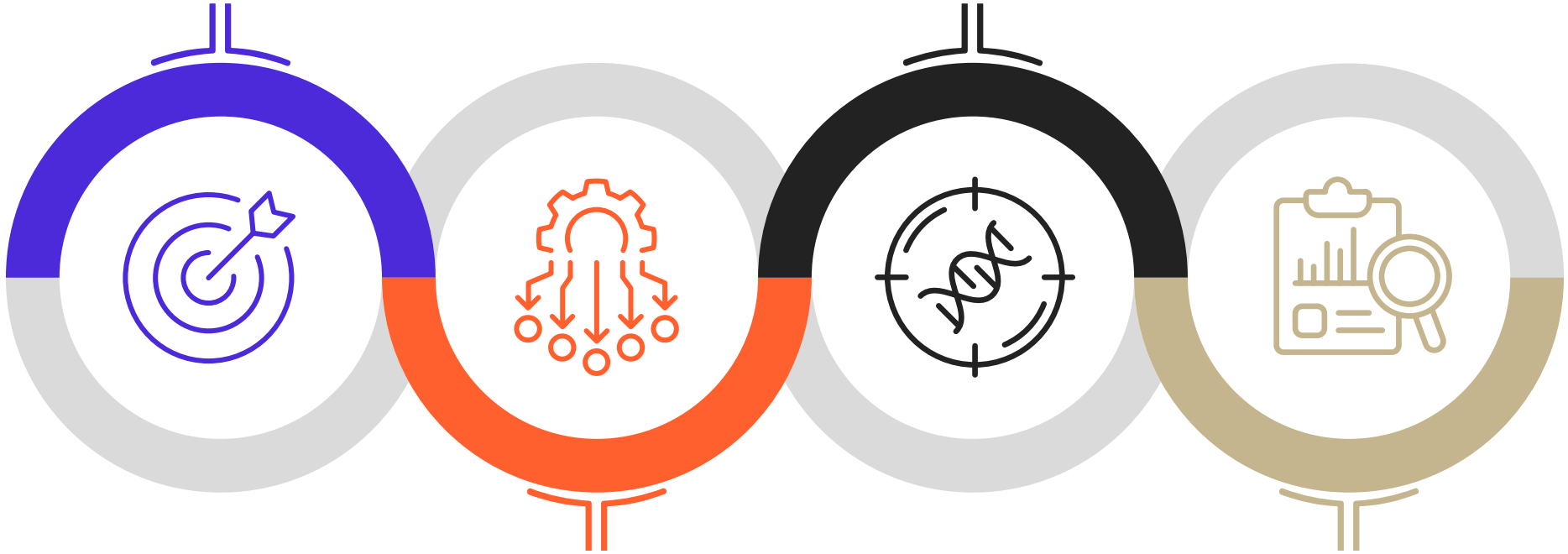
AnQur

Target engagement

- STMN2 levels

Biomarkers of neuronal loss

- NfL and other exploratory biomarkers



Mechanism of action (MOA)

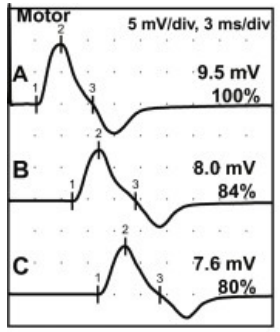
- Motor excitability recordings (CMAP, M-Scan)
- Established NMJ innervation measurements (STMN2 MOA / efficacy)

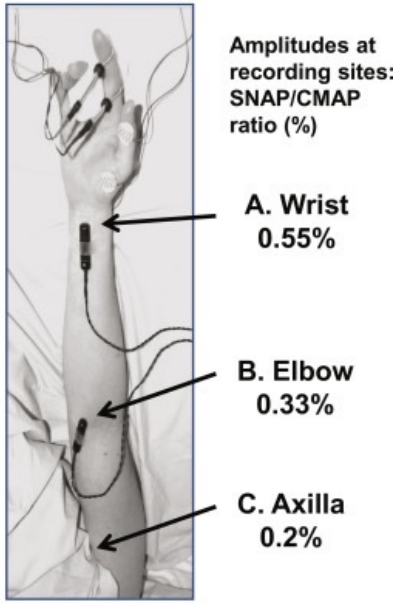
Clinical measurements

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

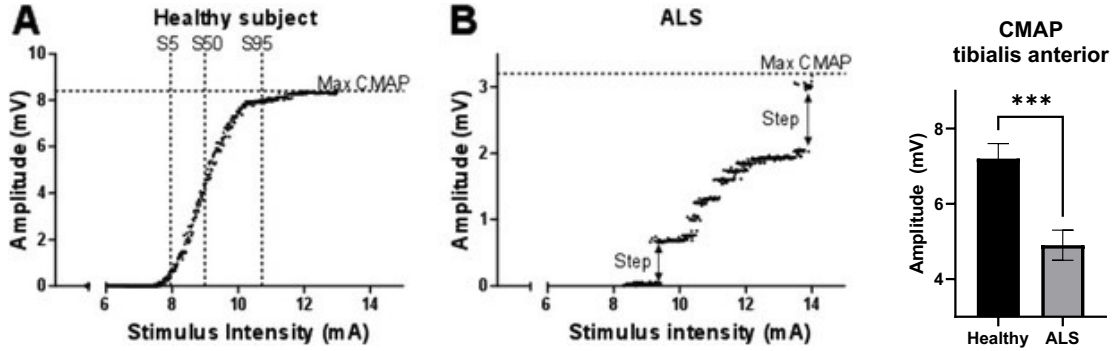
CMAP is a powerful disease progression and efficacy biomarker that measures muscle innervation in ALS

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

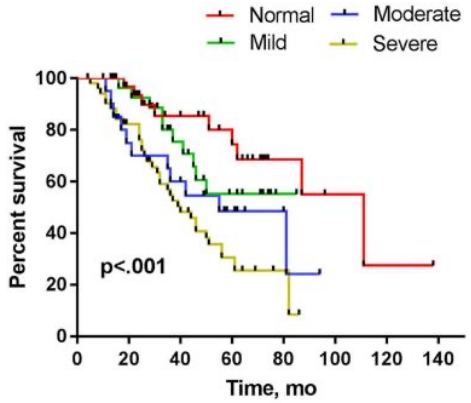




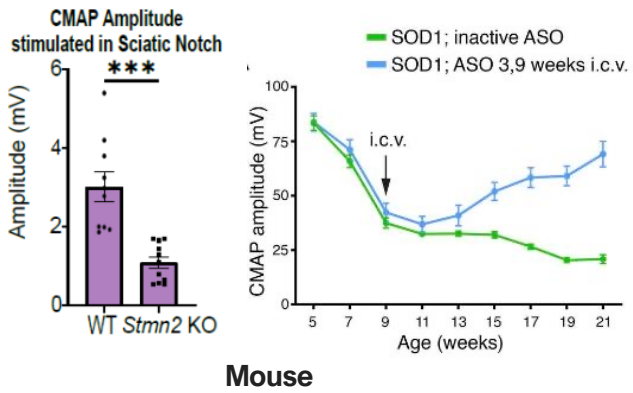
CMAP is used to monitor disease progression in ALS patients



CMAP amplitude predicts survival in ALS



CMAP amplitude can show therapeutic effect of ASO

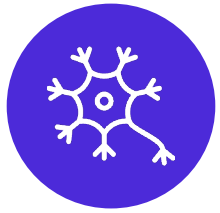


1. Clarissa Crone, Christian Krarup, in *Handbook of Clinical Neurology*, 2013
2. Maathuis et al., 2013 *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2013; 14: 217–223
3. Yu et al., 2021 *Front Neurol*. 2021 Feb 11;12:574919. doi: 10.3389/fneur.2021.574919
4. McCampbell et al., 2018 *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-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 interim efficacy marker & safety data expected H1 2026
Next Ph2 / Ph3 study is a potential registrational study

Ion Channel Recovery

Ion channel dysfunction is implicated across wide range of CNS disorders

Kv7.2/3 channel openers have validation across variety of diseases

- 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
- Further validation of Kv7.2/3 in epilepsy has been demonstrated by XEN1101 and other clinical programs
- Kv7.2/7.3 compound flupirtine was also approved in Europe for 6 different pain indications

- QurAlis is developing QRL-101, a highly selective Kv7.2/3 channel opener:
  - High affinity to Kv7.2/3
  - Lack of affinity for GABA-A receptors and other Kv7 subtypes
  - Human target engagement observed in Phase 1 studies relevant for ALS, epilepsy, and pain

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

Proof of mechanism in healthy volunteers (QRL-101-05)

Evidence of both central & peripheral target engagement

- **mNETT (Threshold Tracking) (ALS / Pain)** → Inhibition of nerve excitability
  - Several measures were significantly altered by QRL-101 demonstrating inhibitory effects on peripheral nerve excitability
  - SDTC, Rheobase, and several other measures appeared to have a dose dependent response
- **Passive EEG (Epilepsy)**
  - Clear central activation/brain penetration with several EEG measures impacted → Target engagement & brain penetration
  - Little to no activation of the slow wave frequency (delta and theta) associated with sedation and GABA-A activation → No sedative effects
- **TMS-EMG & TMS-EEG (ALS / Epilepsy)**
  - ICF TMS-EMG had statistically significant change with QRL-101 treatment → Effect inhibition/ excitability ratio
  - Statistically significant changes to TMS Evoked Potential (TEP) → Target engagement & brain penetration
- **Safety & tolerability**
  - Adverse event (AE) profile consistent with prior studies of QRL-101, no serious AEs or discontinuations due to AEs
  - No clinically meaningful signal of somnolence or persistent dizziness has been observed in any study of QRL-101 to date
  - Formulation work has resulted in lower cMax, while maintaining AUC, to alleviate GI AEs seen with liquid formulation

CONTEXT

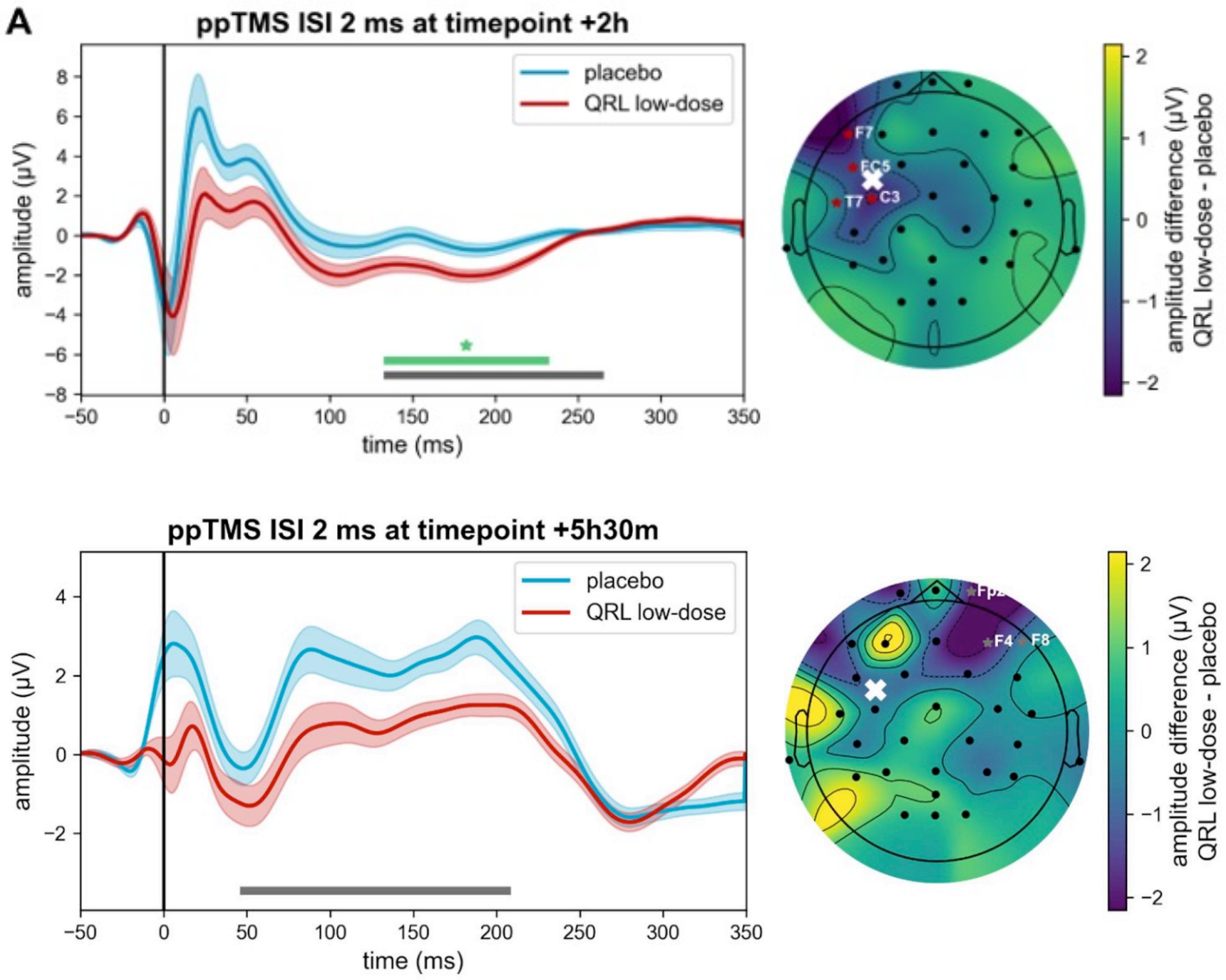
Summary of analysis results – strong biomarker readouts for epilepsy, pain, and ALS

		p-value treatment v. placebo	
Indication	**PD measure**	**Low Dose**	**High Dose**
Pain/ALS	Refractoriness at 2.5 ms (%)	<0.0001	<0.0001
Pain/ALS	Refractory period (ms)	0.0002	<0.0001
Pain/ALS	Superexcitability (%)	0.001	<0.0001
Pain/ALS	Superexcitability at 7 msec (%)	0.0016	<0.0001
Pain/ALS	Superexcitability at 5 msec (%)	0.0024	<0.0001
Pain/ALS	Strength-Duration Time Constant (ms) SDTC	0.0039	<0.0001
Pain/ALS	Hyperpolarizing I/V-slope	0.0057	<0.0001
Pain/ALS	Stimulus-Response\Slope	0.0128	0.0001
Pain/ALS	Subexcitability (%)	0.0091	0.0002
Pain/ALS	Accommodation Half-Time (ms)	0.03	0.0011
Pain/ALS	Refractoriness at 2 ms (%)	0.0001	0.0019
Pain/ALS	Rheobase (mAmp)	0.3858	0.0068
Pain/ALS	TEd40-60 (%)	0.3991	0.0221
Pain/ALS	Resting I/V-Slope	0.3635	0.0237
Pain/ALS	Motor Stimulus for 50% max response or Threshold Current (mAmp)	0.6093	0.0285
Epilepsy/ALS	TMS-EMG Intracortical Facilitation (ICF) at 15 ms (%)	0.0071	0.0486
Epilepsy	TMS-TEP 0-300ms	0.001	0.03
Epilepsy	TMS-TEP N100	0.02	0.002
Epilepsy	TMS-TEP P180	0.002	0.06
Epilepsy	EEG Beta-power Fz-Cz eyes closed (dB)	0.0318	0.0067
Epilepsy	EEG Gamma-power Pz-O2 eyes closed (dB)	0.0154	0.0083

p-value <0.05

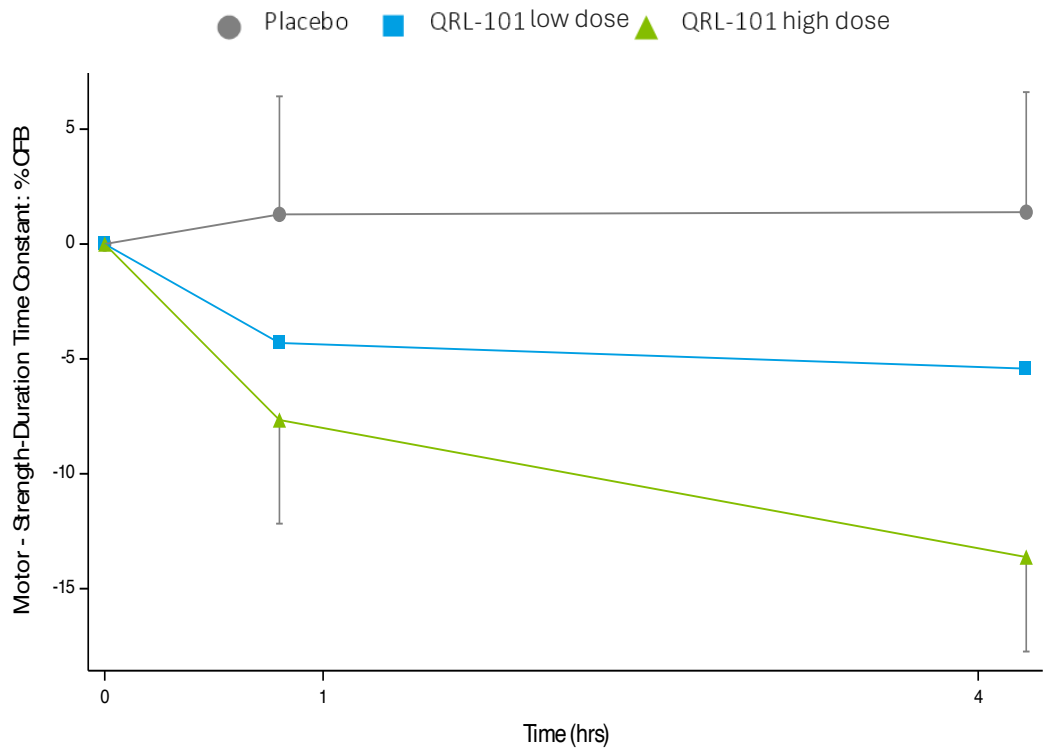
QRL-101 delivered statistically significant dose responsive pharmacodynamic changes across multiple peripheral and central electrophysiology endpoints with minimal tolerability issues

QRL-101 shows inhibition in TEP measurements even at the low dose of the PoM study

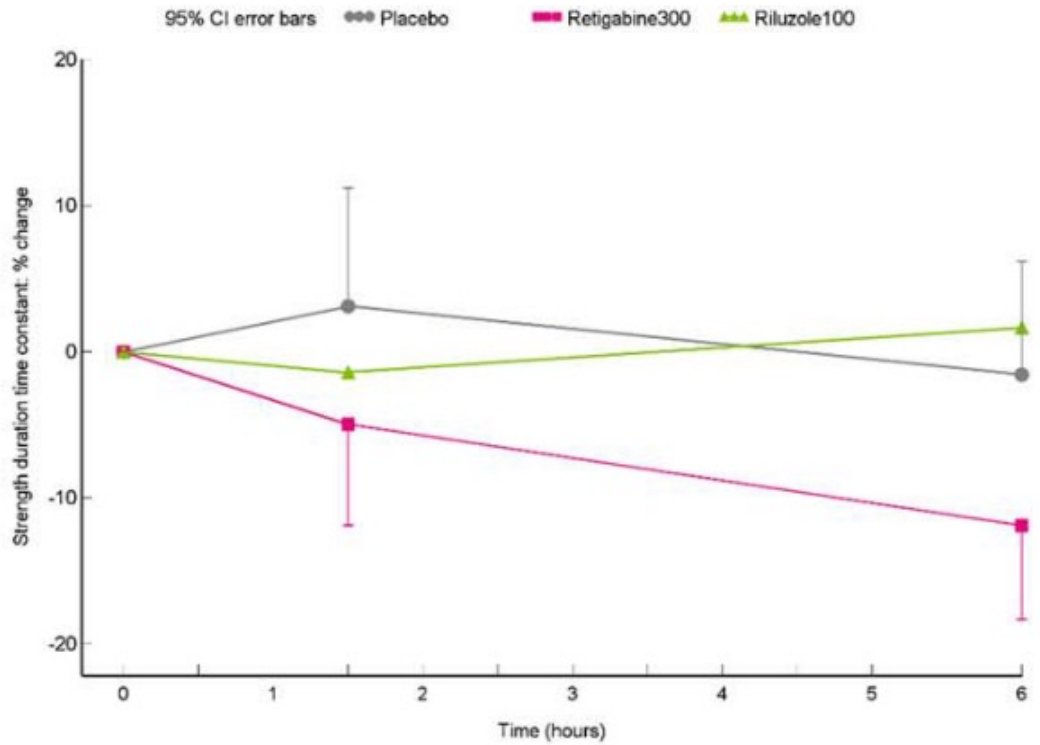


QRL-101 is ~50% more potent than retigabine/Ezogabine on peripheral excitability biomarker SDTC in humans

Strength-Duration Time Constant (% CFB)



Strength-Duration Time Constant (% CFB)

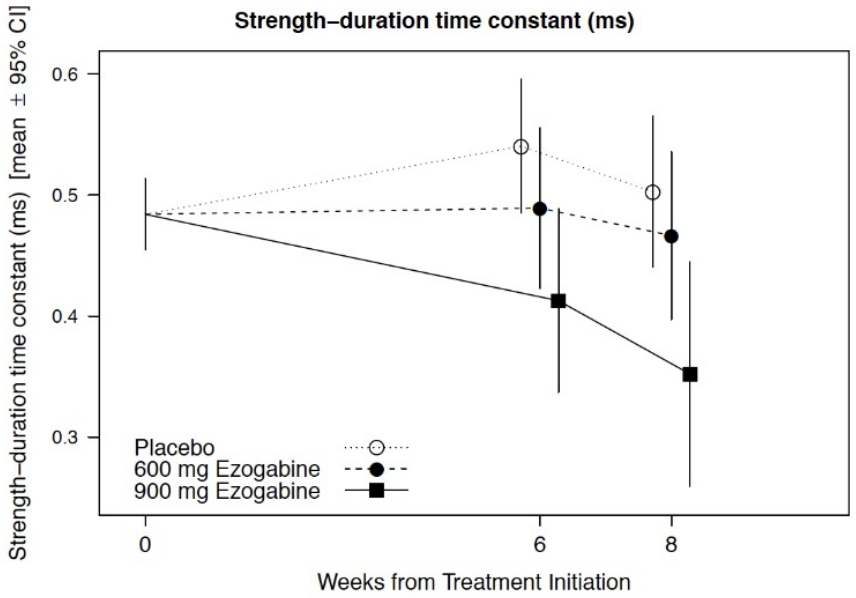


300mg retigabine is single dose, equivalent to 900mg total daily dose in POTIGA FDA label

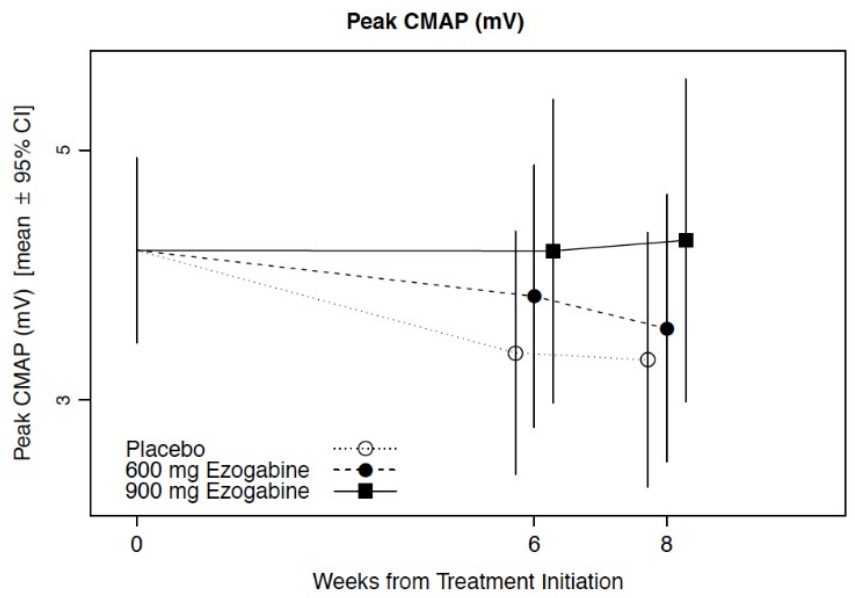
Kv7 is a clinically validated target in ALS

Ezogabine published trial results[1] (n= 65 patients) validated the importance of reducing hyperexcitability through Kv7

Statistically significant[2] dose-dependent effects on biomarkers that predict patient survival



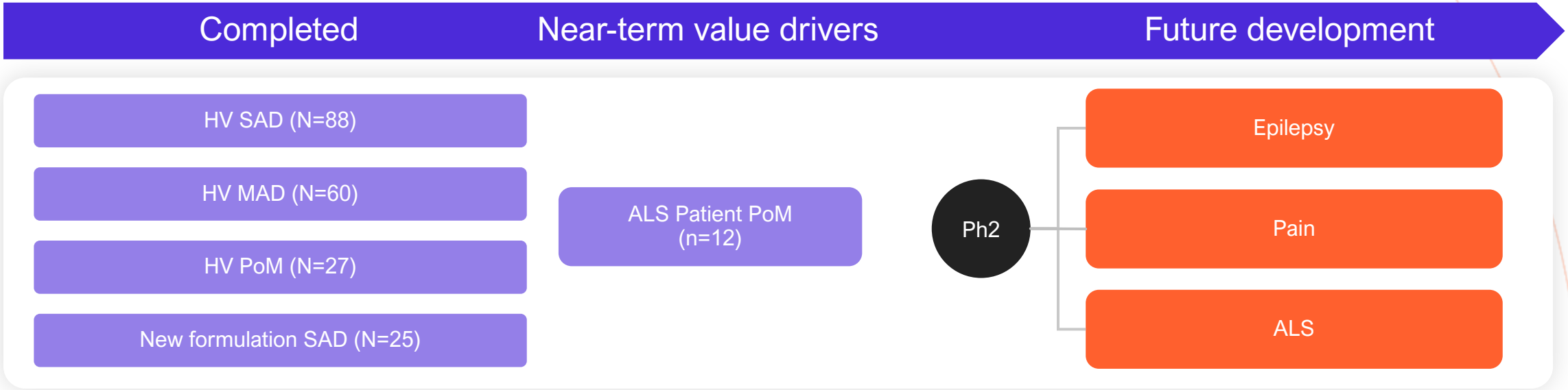
Statistically significant[2] impact on critical disease progression & efficacy biomarker (CMAP)



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

[1]Wainger BJ, Macklin EA, Vucic S, et al. *JAMA Neurol.* 2021;78(2):186–196. doi:10.1001/jamaneurol.2020.4300
[2]Error bars from JAMA paper represent standard deviations, results are statistically significant

Phase 1 data package supports advancement into epilepsy, pain, and ALS



Key findings

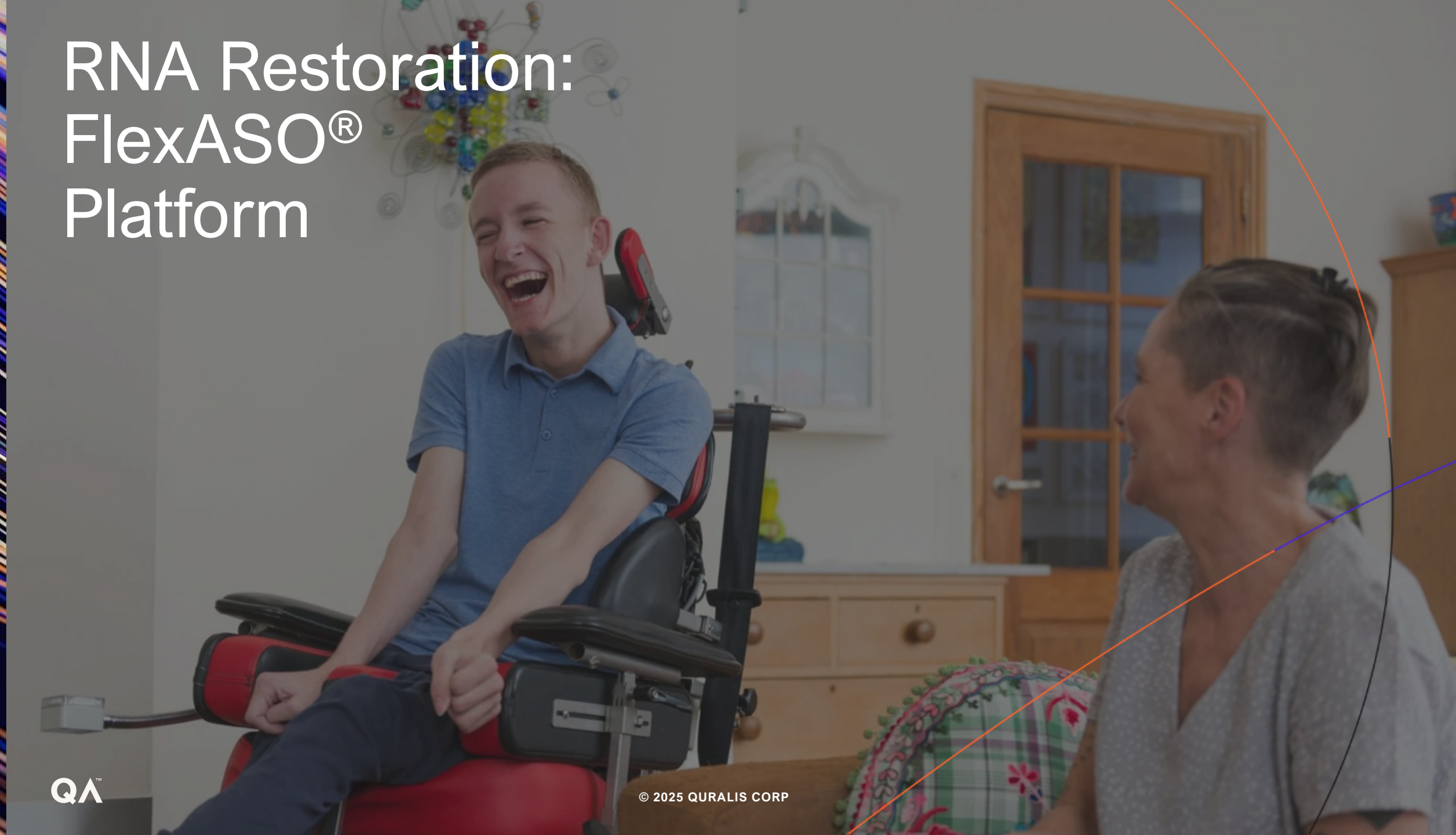
- Generally well tolerated, large majority of AEs were mild in nature, no treatment-emergent SAEs
- New formulations demonstrates decrease in cMax and increase AUC compared to liquid
- Biomarker validation across multiple disease models in HVs (ALS, Pain, Epilepsy)

Key outcomes

- Biomarker validation in ALS patients

SAD: Single Ascending Dose; MAD: Multiple Ascending Dose; PoM: Proof of Mechanism; PoC: Proof of Concept; PK/FE: Pharmacokinetics / Food Effect; HVs: Healthy Volunteers

RNA Restoration: FlexASO® Platform



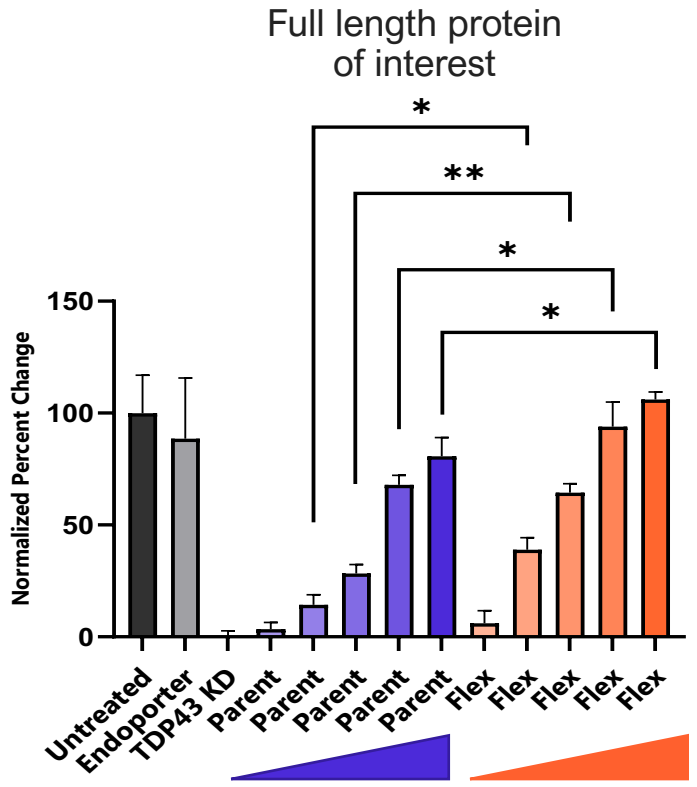
Flex ASO® is the leading splice-modulation platform to restore RNA

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

Attributes	Flex ASO	Traditional ASO
Size	✓	✓
Therapeutic Effect	✓ ✓	✓
Toxicity	✓ ✓	✓
CMC	✓	✓
Distribution	✓ ✓	Known for spinal cord and frontal cortex

Potential to overcome modality-specific, dose-limiting toxicities

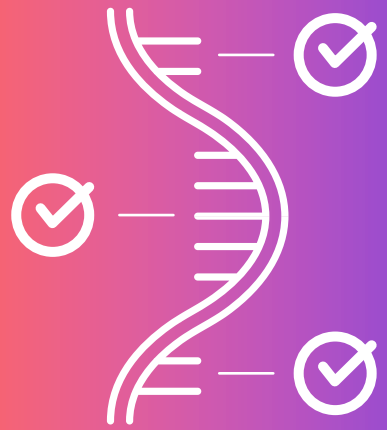
FlexASO® demonstrates statistically significant increase in RNA restoration vs. parent



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

Technological breakthroughs

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



Disease-modifying RNA therapies

RNA restoration oligonucleotides targets

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

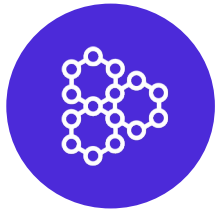
Driving scientific breakthroughs into powerful precision medicines

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 programs in the clinic with near-term data readouts

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

Proprietary FlexASO® platform can potential expand to additional RNA restoration therapies

World-class team to execute

Experienced executive team

UNC13A partnership with Lilly underscores value of FlexASO® platform

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

Thank you

For more information contact:
Kasper Roet (CEO & Cofounder)
kasper.roet@quralis.com

Jason Brown (CFO)
jason.brown@quralis.com