QRL-101 – Phase 1 Studies Evaluating Safety and Pharmacodynamics of a KCNQ2/3 Modulator in Healthy Volunteers & Next Steps for Development in ALS

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INTRODUCTION

- Amyotrophic lateral sclerosis (ALS) is a rare, adult-onset neurodegenerative disease resulting primarily in loss of motor neurons in the motor cortex, brainstem, spinal cord, and peripheral nerves, with often rapid functional decline, and death typically resulting from respiratory failure. The median survival from disease onset is 2 to 5 years. There is no cure for ALS, and currently approved therapies only provide modest benefits for people living with ALS.[1]
- In ALS, increased cellular excitability can be observed in both peripheral and central motor neurons. Clinically this presents as fasciculations, muscle cramps, hyper-reflexia and spasticity. The presence of increased persistent hyperexcitability has been shown to correlate with more rapid functional decline and shorter overall survival.[1]
- KCNQ2/KCNQ3 potassium channels (Kv7.2-Kv7.3) were found to play a critical role in controlling membrane excitability in both human stem cell-derived and primary mouse spinal motor neurons.[2,3] KCNQ2 is mis-spliced in sporadic ALS leading to loss of function.
- QurAlis' therapeutic approach with QRL-101 is to reduce abnormal electrical activity in the brain by activating or opening the Kv7.2/7.3 ion channel to decrease spinal and cortical motor neuron excitability in people living with ALS.

METHODS

- To date the QRL-101 development program consists of 5 Phase 1 studies in approximately 212 participants.
- **QRL-101-01:** first-in-human, single-ascending dose (SAD) study in 88 healthy participants. (ClinicalTrials.gov ID: NCT05667779)
- **QRL-101-03:** multiple-ascending dose (MAD) study in 60 healthy participants. (ClinicalTrials.gov ID: NCT06532396)
- **QRL-101-04:** proof-of-mechanism PK/PD study in approximately 12 participants with ALS. (ClinicalTrials.gov ID: NCT06714396)
- **QRL-101-05:** proof-of-mechanism PD study in 27 healthy participants. (ClinicalTrials.gov ID: NCT06681441)
- **QRL-101-06:** PK study to evaluate multiple formulations and food effect in 25 healthy participants. (ClinicalTrials.gov ID: NCT06877624)

Completed | **Ongoing***

- QRL-101-01 HV SAD (N=88)
- QRL-101-03 HV MAD (N=60)
- QRL-101-05 ALS & Epilepsy PoM in HVs (N=27)
- QRL-101-04 ALS Patient PoM (n=12)
- QRL-101-06 New Formulation Food Effect (N=25)

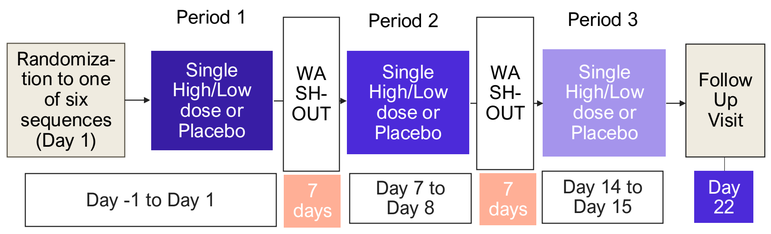
*Results expected later this year.

QRL-101 PHASE I STUDIES: KEY FINDINGS

- QRL-101 at single or multiple doses is generally safe and well tolerated
- Majority of AEs were mild in nature
- No treatment-emergent SAEs reported
- No findings of clinical relevance with respect to clinical laboratory parameters, vital signs, 12-lead ECGs, physical examinations, or C-SSRS
- Pharmacodynamic marker validation across multiple disease relevant biomarkers in HVs

QRL-101-05 STUDY DESIGN

Study Schematic: A Phase I, Randomized, Double-blind, Placebo-controlled, 3-way Cross-over Study to Assess the Pharmacodynamic Effects of Two-dose Levels of QRL-101 on Transcranial Magnetic Stimulation (TMS) and Nerve Excitability Threshold Tracking (NETT) in Healthy Participants



Screening period up to Day -42

PD endpoints measured in each period:

- EEG pre dose and 2x post-dose
- TMS-EMG pre-dose and 2x post-dose
- NETT pre-dose and 2x post-dose
- Several PK sampling timepoints up to 24h post dose

QRL-101-05 PHARMACODYNAMIC RESULTS

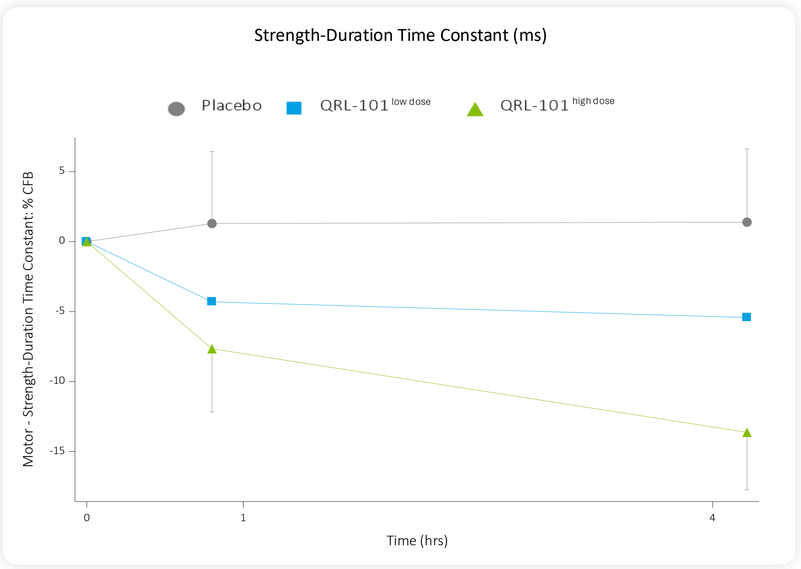
QRL-101 delivered statistically significant dose responsive pharmacodynamic changes across multiple peripheral and central electrophysiology endpoints with minimal tolerability issues.

PD measure	Measure	p-value treatment v. placebo: High Dose	Low Dose
Refractoriness at 2.5 ms (%)	NETT	<0.0001	<0.0001
Refractory period (ms)	NETT	0.0002	<0.0001
Superexcitability (%)	NETT	0.001	<0.0001
Superexcitability at 7 msec (%)	NETT	0.0016	<0.0001
Superexcitability at 5 msec (%)	NETT	0.0024	<0.0001
Strength-Duration Time Constant (ms) SDTC	NETT	0.0039	<0.0001
Hyperpolarizing I/V-slope	NETT	0.0057	<0.0001
Stimulus-Response\Slope	NETT	0.0128	0.0001
Subexcitability (%)	NETT	0.0091	0.0002
Accommodation Half-Time (ms)	NETT	0.03	0.0011
Refractoriness at 2 ms (%)	NETT	0.0001	0.0019
Rheobase (mAmp)	NETT	0.3858	0.0068
TEd40-60 (%)	NETT	0.3991	0.0221
Resting I/V-Slope	NETT	0.3635	0.0237
Motor Stimulus for 50% max response or Threshold Current (mAmp)	NETT	0.6093	0.0285
TMS-EMG Intracortical Facilitation (ICF) at 15 ms (%)	TMS-EMG	0.0071	0.0486

QRL-101-05 PHARMACODYNAMIC RESULTS CONT'D

The dose levels assessed resulted in exposure levels that exceed those anticipated to be required for target engagement. The electrophysiology endpoints utilized allowed assessment of the potential PK-PD relationship for QRL-101.

QRL-101 delivered statistically significant dose responsive change in ALS biomarker, Strength Duration Time Constant (SDTC).



QRL-101-05 SUMMARY OF RESULTS

ALS Related	• Several measures MNETT (threshold tracking 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. • QRL-101 appears to be more potent than retigabine/Ezogabine on the SDTC biomarker in humans which predicts patient survival in ALS*. • TMS-EMG ICF measurements show a significant change with QRL-101 treatment, indicating effective inhibition of excitability in the brain. • Evidence of a positive trend in other TMS measures. • Little to no activation of slow wave frequencies (delta & theta) associated with sedation and GABA-A activation.
Experi-mental Consider-ations	• PD measures were normalized to the baseline measure taken at the start of each day in clinic; this was done for every PD measure. • Timing of TMS measures in relation to Cmax had an impact on some measures.
Safety & Formula-tion Related	• QRL-101 was generally well tolerated. All TEAEs reported were mild or moderate in severity; No TESAEs reported. • Plasma PK exceeds putative target efficacy levels for 3 hours to 5 hours after dosing at the high dose.

*These measurements were conducted by the same CRO.

CONCLUSIONS

- Results of these studies support initiation of a Phase 2 POC study in ALS, planned for the near future. A safe and tolerable dose range has been determined.
- Reducing motor system hyperexcitability is a potential therapeutic strategy in ALS.
- Electrophysiology endpoint results support continued use of these measures as markers of target engagement. These studies have used an operational framework of fit-for-purpose, exploratory electrophysiology endpoints.
- These endpoints may be scalable to other, larger, multi-center, global clinical trials. Findings from these studies will be used to advance the development of QRL-101 in ALS and other neurodegenerative diseases.

REFERENCES

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