Evaluating the Safety, Tolerability, and Pharmacokinetics of QRL-101 in Two Phase 1 Studies: QRL-101-01 in Healthy Adults and QRL-101-02 in Adults Living With ALS

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BACKGROUND

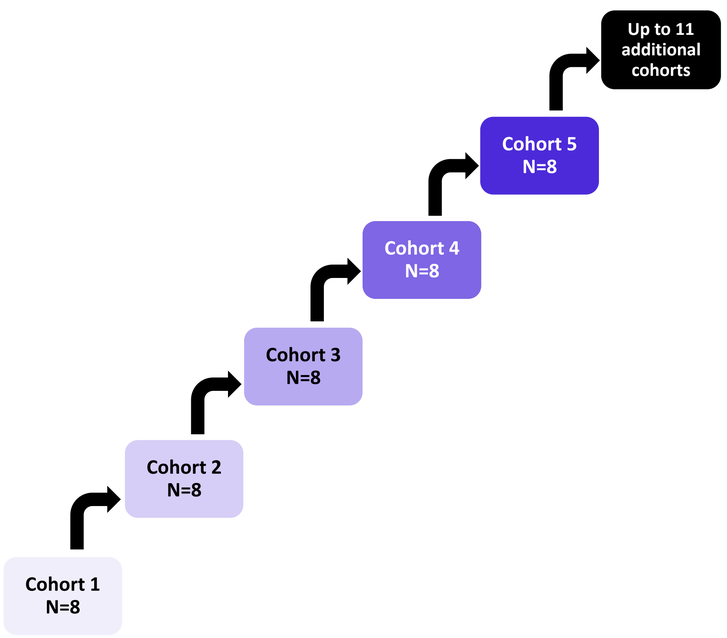
- Amyotrophic lateral sclerosis (ALS) is a rare, adult-onset neurodegenerative disease resulting primarily in loss of motor neurons in the motor cortex, brainstem, spinal cord, and peripheral nerves, with often rapid functional decline, and death typically resulting from respiratory failure. The median 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]
- Our 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.

INTRODUCTION

- The safety, tolerability, and pharmacokinetics (PK) of QRL-101 will be evaluated in two, consecutive, randomized, placebo-controlled, double-blind, phase 1 studies.
- **QRL-101-01**, is an ongoing first-in-human, single-ascending dose (SAD) study in up to 128 healthy participants randomized in a 6:2 ratio of study drug to placebo.
- Information from QRL-101-01 will be used to determine a safe and tolerable dose range for a subsequent, planned, multicenter multiple-ascending dose (MAD) study, **QRL-101-02**, to evaluate QRL-101 in adults living with ALS. Both studies will utilize a sentinel dosing strategy, as well as multiple safety reviews.

QRL-101-01 STUDY DESIGN

- Single-ascending doses of QRL-101 or placebo will be orally administered to a planned maximum of 128 healthy participants, in up to 16 cohorts of 8 participants each, randomized 6:2 (QRL-101: placebo).



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QRL-101-01 STUDY OBJECTIVES & ENDPOINTS

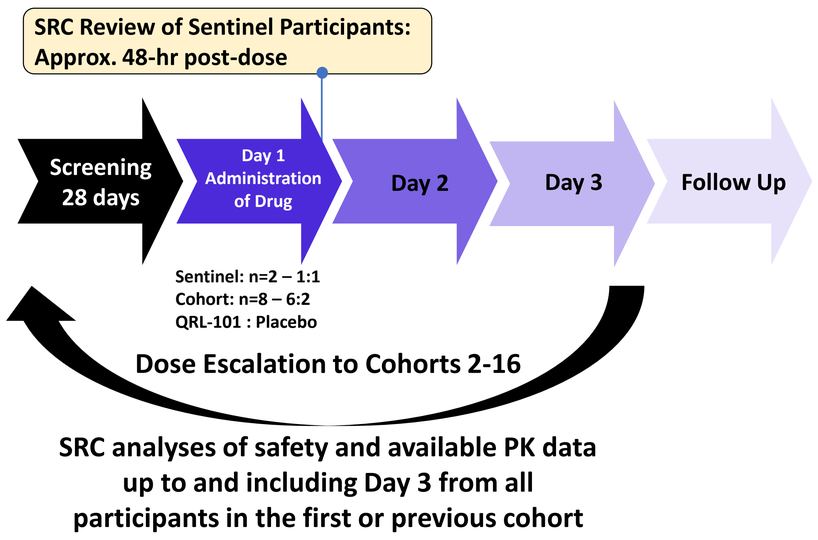
Primary Objective	Primary Endpoints
To determine the safety and tolerability of QRL-101 after a single oral dose in healthy participants	• AEs • SAEs
Secondary Objective	**Secondary Endpoints**
To determine the PK profile of QRL-101 after a single oral dose in healthy participants	• AUC_{0-24} • C_{max} • T_{max}

Abbreviations: AEs = adverse events; SAEs = serious adverse events; AUC_{0-24} = area under the curve from 0 to 24 h; C_{max}= maximum concentration; T_{max}= time of maximum concentration

QRL-101-01 KEY ELIGIBILITY CRITERIA

Inclusion Criteria	• Male or female participants between the ages of 18 to 70 years • Clinical chemistry laboratory values within acceptable range for the population • Body mass index of 18 to 32 kg/m^2
Exclusion Criteria	• Currently enrolled in any other clinical trial involving a study drug or off-label use of a drug or device, or any other type of medical research judged not to be scientifically or medically compatible with this study. • Any subject who participates in >4 studies a year and/or has participated in a clinical trial within 1 month of expected dosing date. • "Suicidal Ideation" or "Suicidal Behavior" per the Columbia-Suicide Severity Rating Scale (C-SSRS) within the past month. • History or presence of significant medical illness, surgery, drug hypersensitivity or alcoholism.

QRL-101-01 DOSING & SAFETY REVIEWS



SRC = Safety Review Committee

QRL-101-01 SAD STUDY STATUS

- In the 80 participants dosed to date, no significant safety concerns or SAEs have been reported.
- The study is ongoing and is expected to complete in early 2024.
- Further details on the QRL-101-01 study can be found on www.clinicaltrials.gov, NCT05667779

QRL-101-02 MAD STUDY

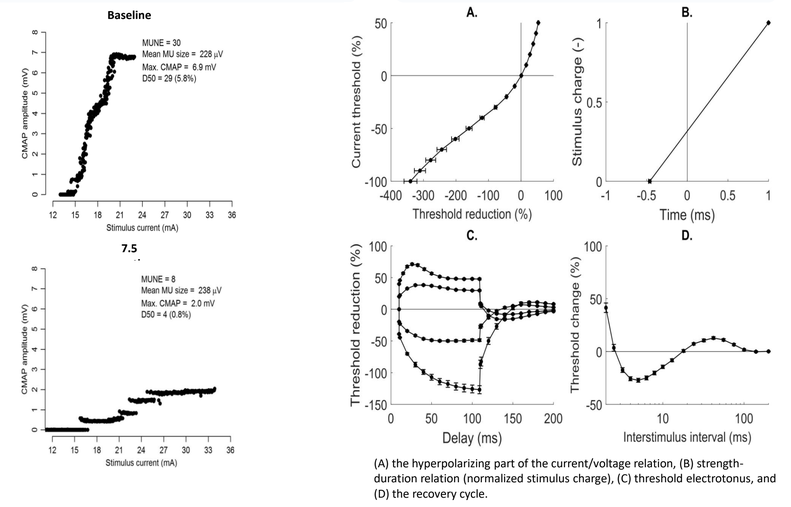
- QRL-101-02 is planned to be a randomized, placebo-controlled, double-blind, multiple ascending dose (MAD) study to evaluate safety, tolerability and PK of QRL-101 in adults living with ALS.
- Additional exploratory endpoints are expected to be evaluated to assess the impact of QRL-101 on clinical outcomes and biomarkers, including electrophysiological markers of motor nerve excitability in people living with ALS.
- Data from the ongoing QRL-101-01 SAD study will determine the start of the MAD study. The study is anticipated to start in 2024. Further information will be posted on www.clinicaltrials.gov.

ELECTROPHYSIOLOGY MODULE

- Altered excitability has been suggested to represent early pathophysiological mechanisms associated with motor neuron death and have been associated with more aggressive disease and shorter survival.
- Axonal excitability measures such as excitability recordings have the potential to serve as translational tools to validate target engagement of compounds that modulate motor neuron excitability (e.g., QRL-101).
- CMAP, M Scan, and hyperexcitability techniques, including threshold tracking, will be performed to evaluate disease progression during the MAD study.

Visual Changes in CMAP Scans During ALS Disease Progression[5]

Baseline Motor Excitability Recordings[6]



(A) the hyperpolarizing part of the current/voltage relation, (B) strength-duration relation (normalized stimulus charge), (C) threshold electrotonus, and (D) the recovery cycle.

- Electrophysiology assessments will be repeated at numerous timepoints over the planned MAD study.
- Data from the electrophysiology assessments may support dose escalation decisions within the MAD and/or a dose selection strategy for future studies.

CONCLUSIONS

- In both studies, the primary and secondary endpoints will be incidence of adverse events and measurements of the PK of QRL-101 at single or multiple doses, respectively.
- The QRL-101-02 study will begin exploring biomarkers and clinical outcomes in relation to multiple doses of QRL-101 in adults living with ALS.
- The findings from these studies will be used to advance the development of QRL-101, and other next-generation precision medicines for people living with ALS and other neurodegenerative diseases.

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