

Qura^{Li}s™

Development of QRL-101
for ALS

Target ALS, May 2025

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:
 - 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 (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 reproducible path to IND and Proof of Concept (PoC)
 - Includes QRL-204 (UNC13A) program licensed to Eli Lilly

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multiple indications including pain, seizure, and mood disorders and marketed for partial-onset seizures before being withdrawn (2017) for undesirable side effect profile, limiting commercial potential
- Ezogabine also demonstrated signal of disease modification in PoM trial in ALS¹, where hyperexcitability is a key characteristic in up to 40-70% of ALS patients



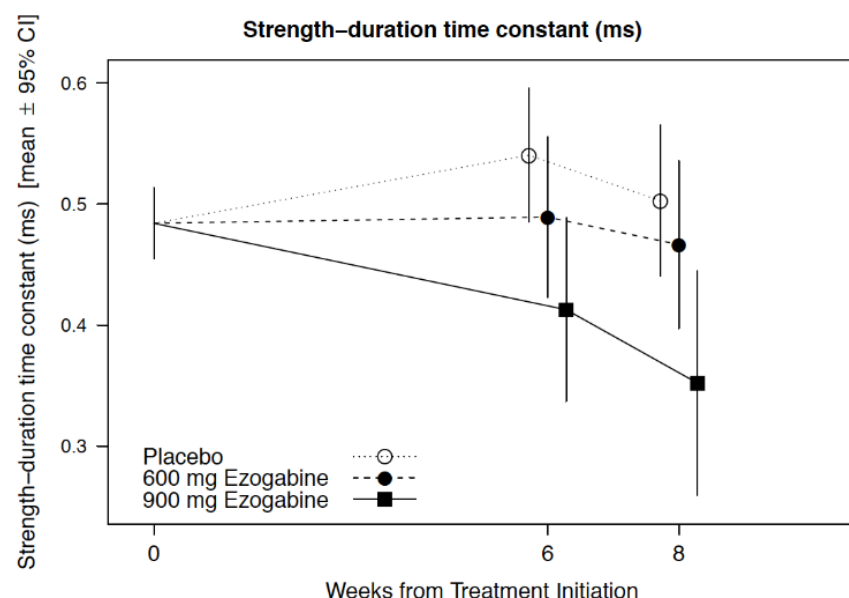
- QurAlis is developing QRL-101, a highly selective Kv7.2/3 channel opener for ALS and epilepsy
 - High potency vs Kv7.2/3
 - Lack of activity vs GABA-A receptors and other Kv7 subtypes
 - Human target engagement observed in Phase 1 studies

¹Wainger BJ, Macklin EA, Vucic S, et al. *JAMA Neurol.* 2021;78(2):186–196. doi:10.1001/jamaneurol.2020.4300

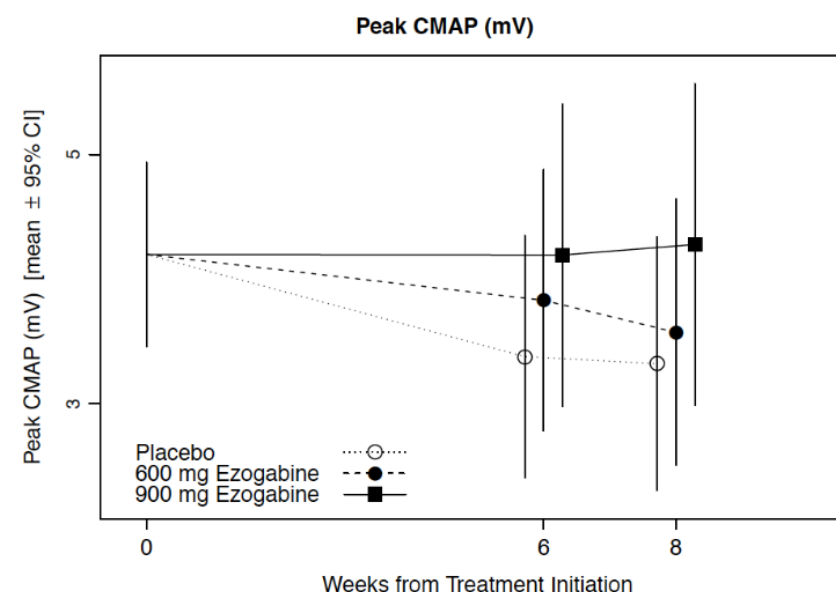
Kv7 is a clinically validated target in ALS

Ezogabine published trial results¹ validated the importance of reducing hyperexcitability through Kv7 (n= 65 patients)

Statistically significant² dose-dependent effects on biomarkers that predict patient survival



Statistically significant² impact on critical disease progression & efficacy biomarker (CMAP)

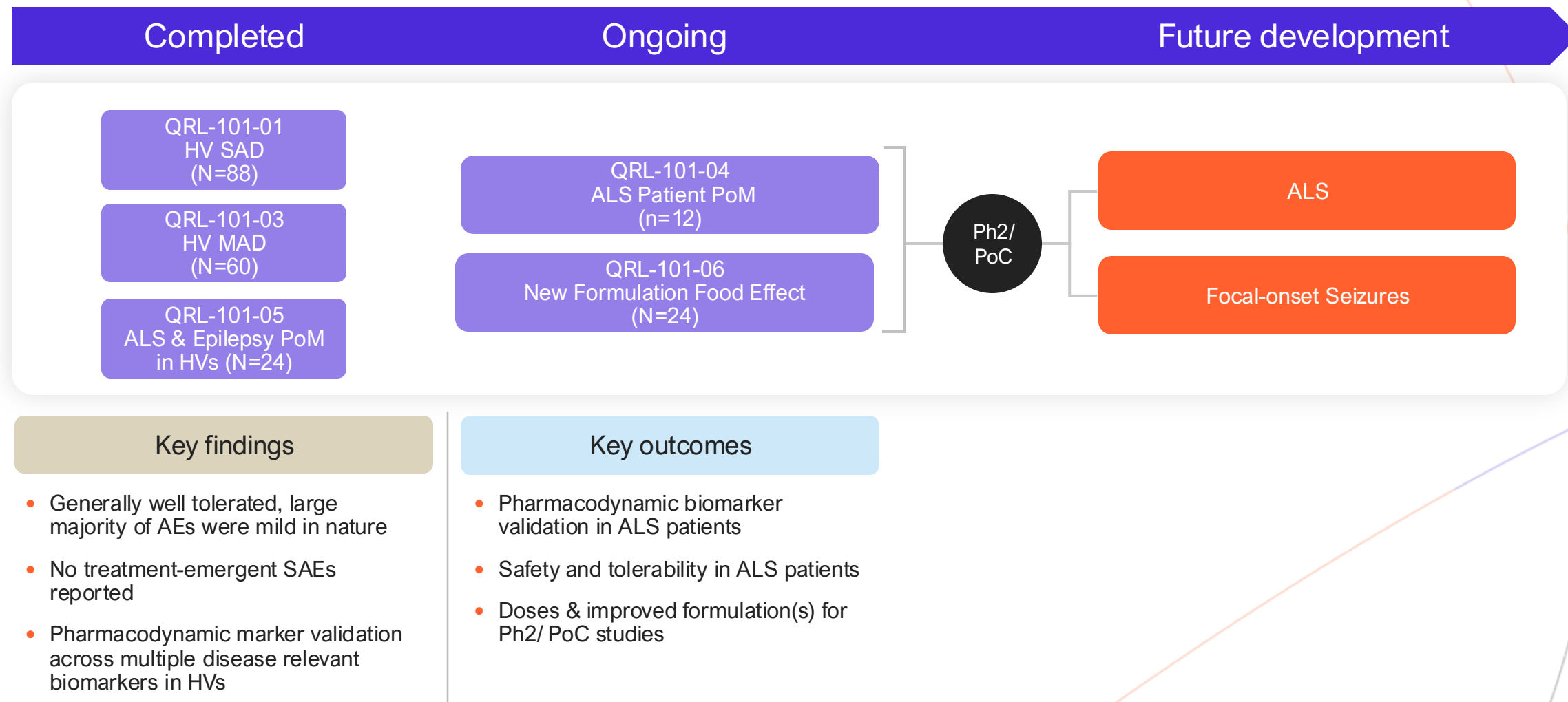


Up to 30% of subjects in ezogabine arms discontinued/ withdrew due to drug tolerability. Most frequent adverse events among participants in the ezogabine arms were fatigue and dizziness

¹Wainger BJ, Macklin EA, Vucic S, et al. *JAMA Neurol.* 2021;78(2):186–196. doi:10.1001/jamaneurol.2020.4300

² Standard deviation, results are statistically significant

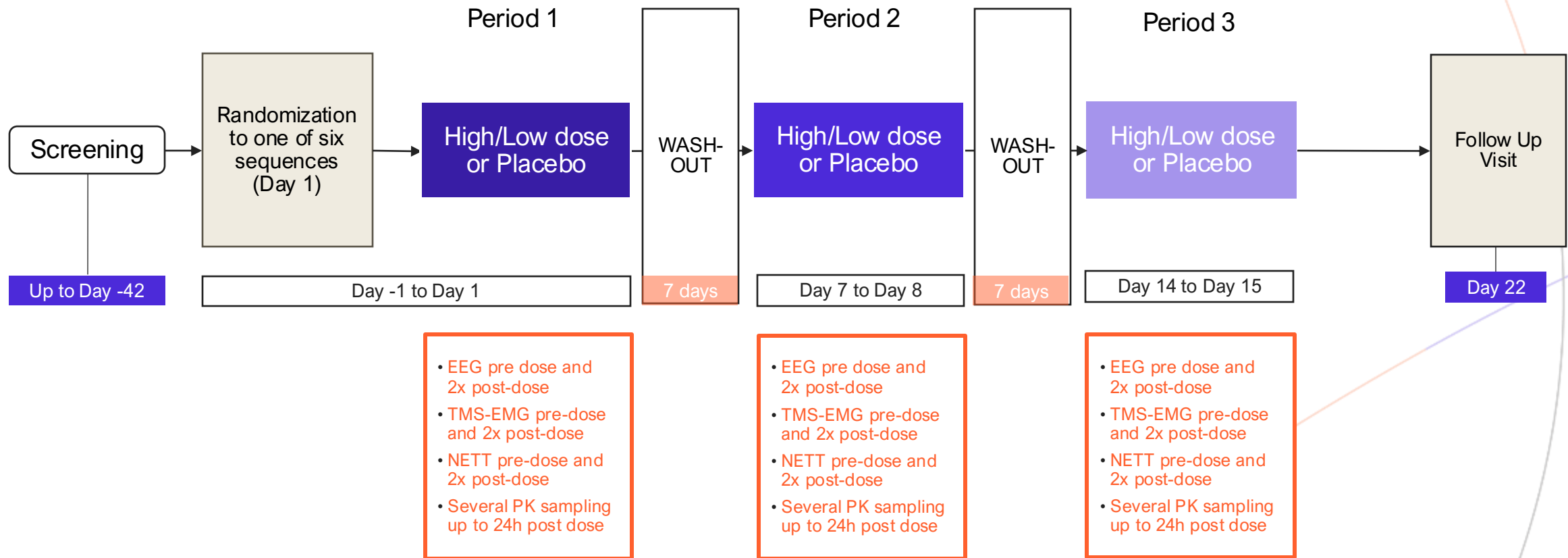
PoM studies for ALS and epilepsy to support dose selection for PoC trials



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

QRL-101-05: Study design (PoM) Ph1 study

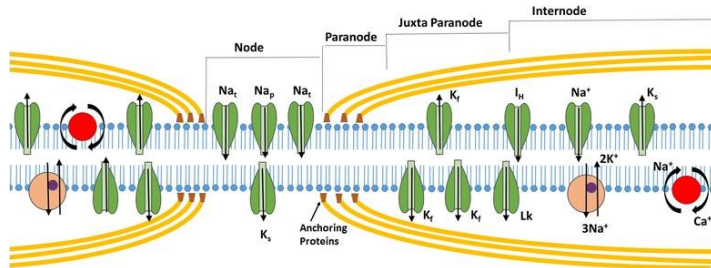
Study Schematic single dose study in healthy volunteers with liquid formulation



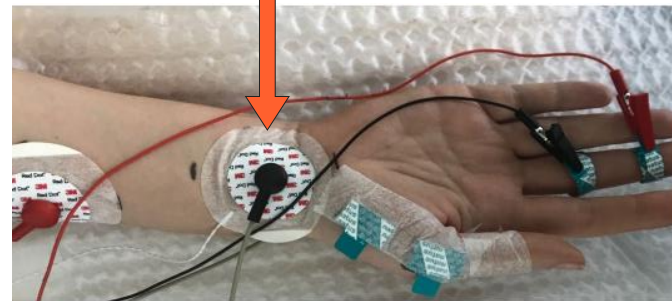
mNETT measures for hyperexcitability

mNETT = motor nerve excitability threshold tracking

- Technique that uses threshold tracking as a way to examine the underlying properties of the axonal membrane and ion channels.
- Includes 4 different tests:
 - Strength-duration (SD), Threshold electrotonus (TE), Current/voltage (I/V), Recovery cycle (RC)



Source: Huynh W, Kieman MC. Peripheral nerve axonal excitability studies: expanding the neurophysiologist's armamentarium. *Cerebellum Ataxias*. 2015;2:4. Published 2015 Mar 3. doi:10.1186/s40673-015-0022-2



Source: CHDR

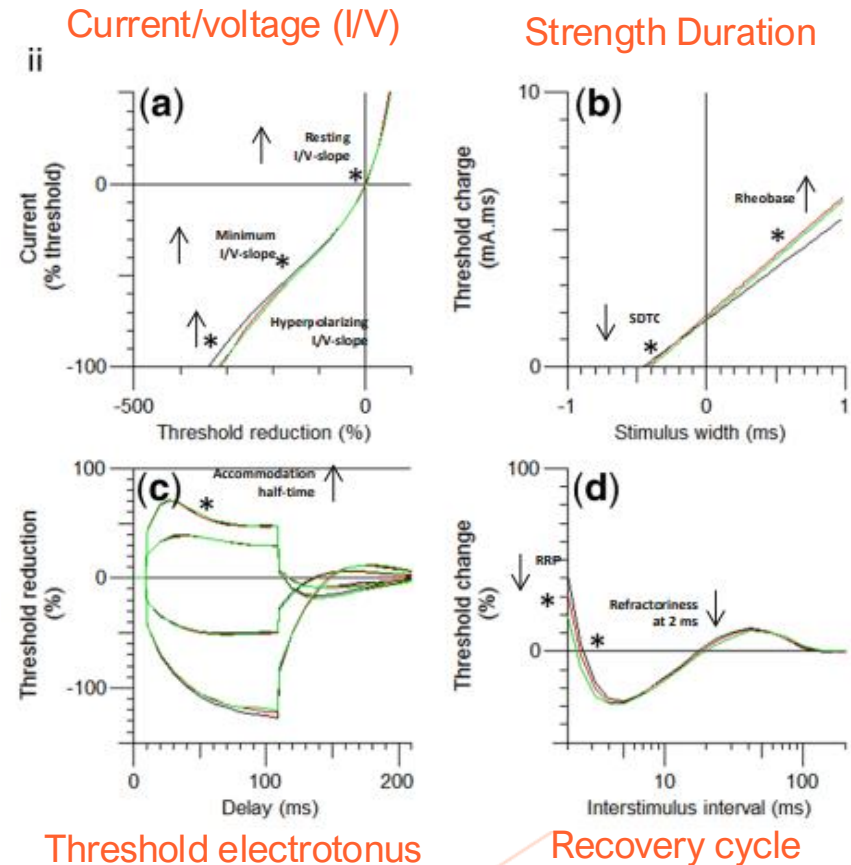
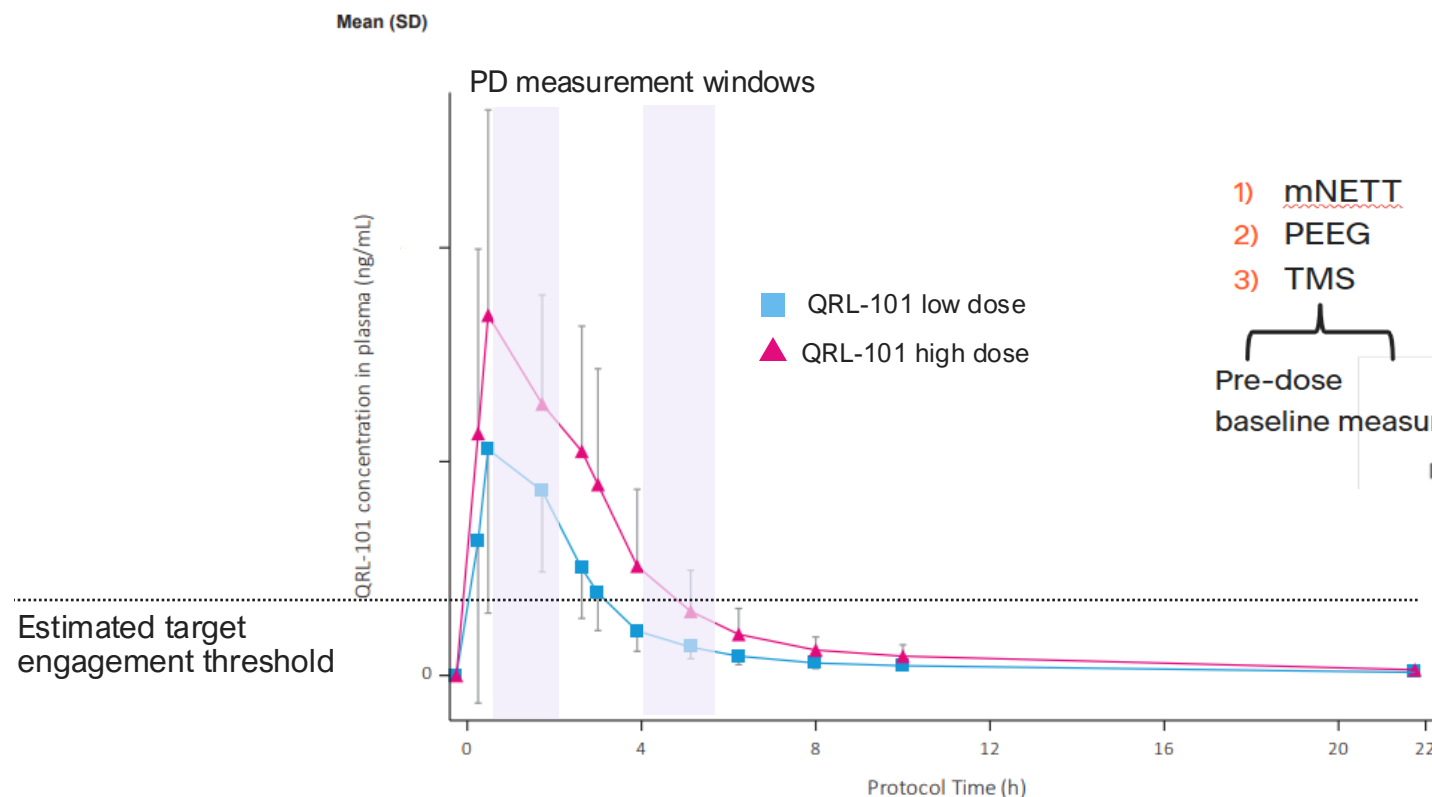


Figure: Mean excitability recordings predose (black), and 1.5 hours (red) and 6 hours (green) after a single dose of 100 mg riluzole (i) and 300 mg retigabine (ii). Asterisks indicate significant treatment effects on thresholds.

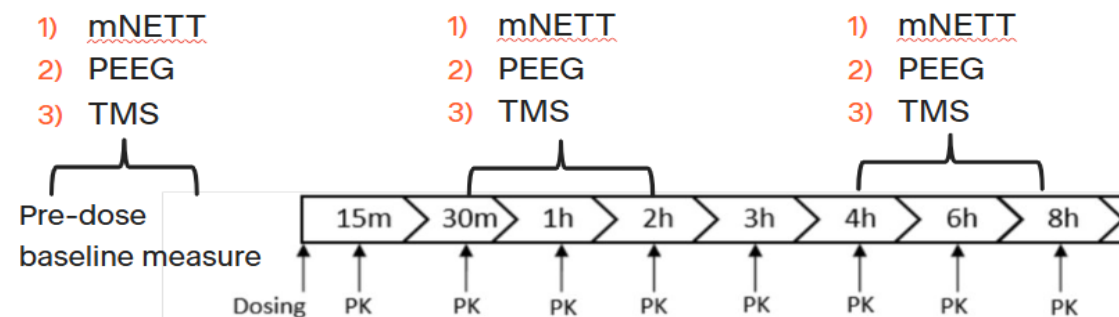
Source: Kovalchuk MO, Heuberger JAAC, Sleutjes BTHM, et al. Acute Effects of Riluzole and Retigabine on Axonal Excitability in Patients With Amyotrophic Lateral Sclerosis: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. *Clin Pharmacol Ther*. 2018;104(6):1136-1145. doi:10.1002/cpt.1096

QRL-101-05 Toplines: PK and PD measurement timing

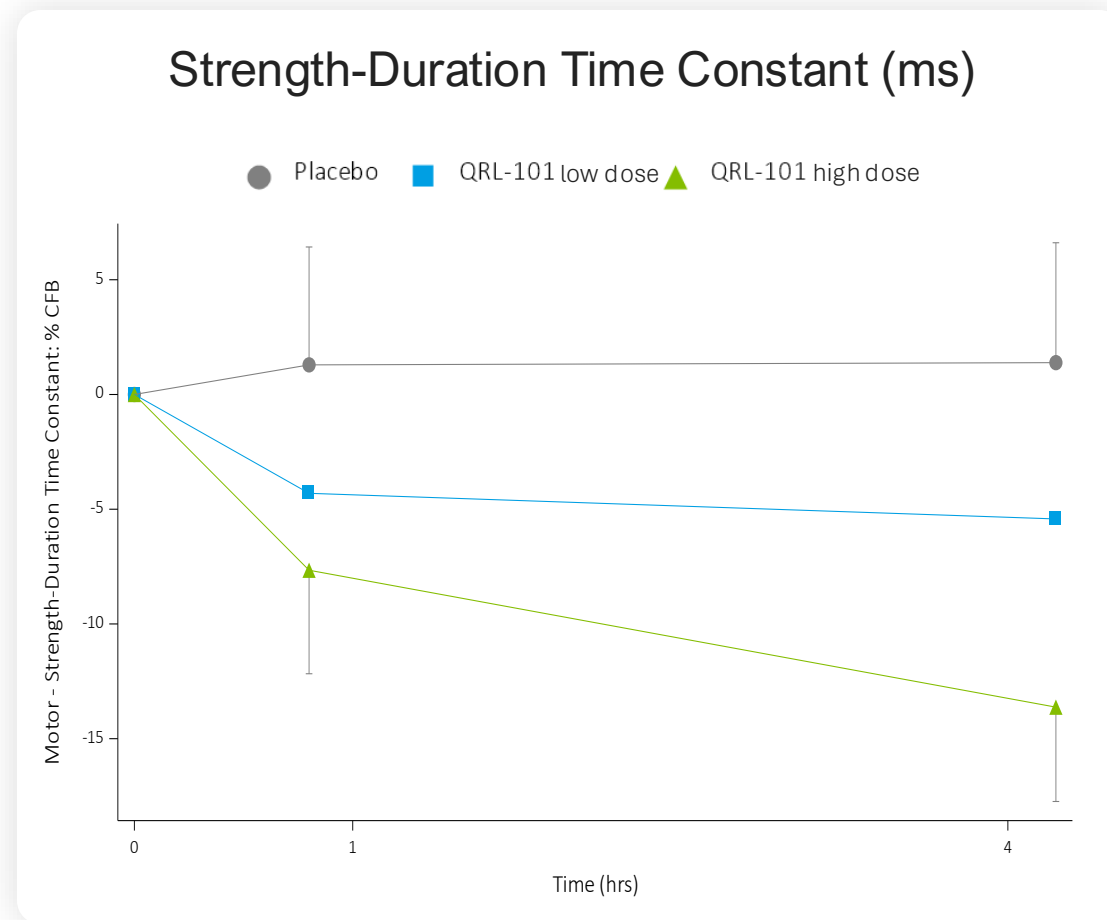
Mean (SD) of QRL-101 Concentration in Plasma (Linear Scale)



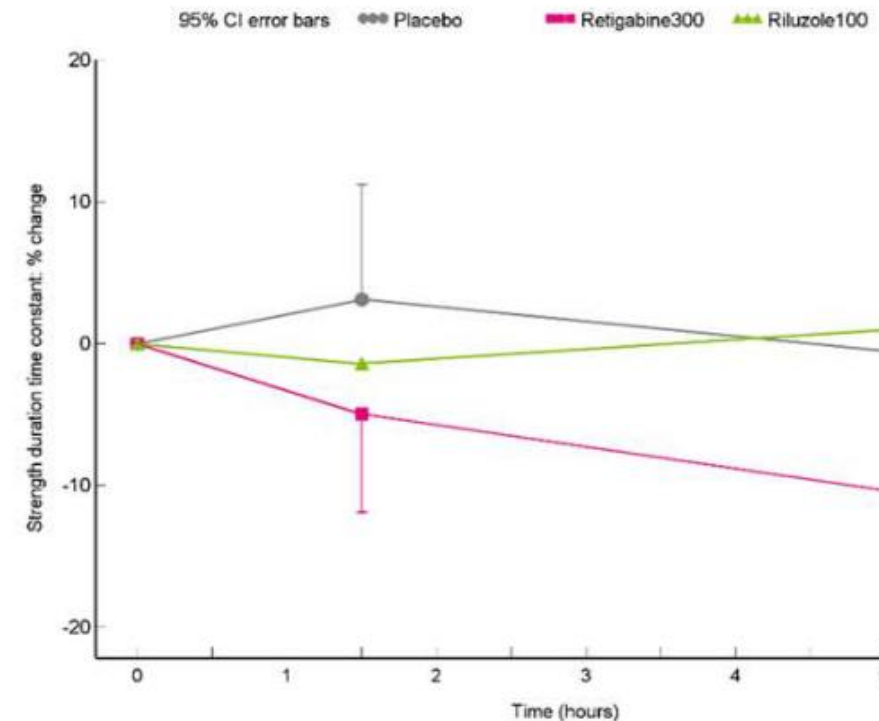
PD Timing and Schedule



QRL-101 was better tolerated and more potent than retigabine/Ezogabine on ALS biomarker SDTC in humans



Strength-Duration Time Constant (%)*



*Kovalchuk MO, Heuberger JAAC, Sleutjes BTHM, et al. *Clin Pharmacol Ther.* 2018;104(6):1136-1145. doi:10.1002/cpt.1096

Lower overall exposure levels for QRL-101 delivered statistically significant dose responsive pharmacodynamic change with minimal tolerability issues

Summary of analysis results - Pharmacodynamic readouts

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

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.
Experimental Considerations	• 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 & Formulation Related	• QRL-101 was generally well tolerated. All TEAEs reported were mild or moderate in severity; No TESAEs reported. • Plasma PK with liquid formulation exceeds putative target efficacy levels for 3 hours to 5 hours after dosing at the high dose.
Next Steps	• QurAlis is planning a PoC in both ALS and Epilepsy with the new formulation.

QRL-101 is generally safe and well tolerated as observed in both non-clinical and clinical studies

- In the QRL-101-01 SAD study, administration of a single dose QRL-101 up to the highest dose tested, was safe and generally well-tolerated in healthy male and female participants.
 - Most TEAEs were mild. There were no SAEs and no findings of clinical relevance with respect to clinical laboratory parameters, vital signs, 12-lead ECGs, physical examinations, or C-SSRS.
- Final clinical study reports have not yet been delivered for QRL-101-03 (MAD) and QRL-101-05 (HV PoM) studies; QRL-101-04 (ALS PoM) is ongoing.
 - QRL-101-03 MAD and QRL-101-05 HV PoM medical data review summaries state that there were no SAEs and no findings of clinical relevance with respect to clinical laboratory parameters, vital signs, 12-lead ECGs, physical examinations, or C-SSRS.
- Chronic NHP toxicology studies are supportive of chronic dosing in humans for QRL-101.



QurAlisTM

Thanks to the sites, staff, investigators, volunteers and patients
who have and continue to support our studies