Quralis™

Driving Scientific Breakthroughs into Powerful Precision Medicines Targeting Major Genetic Disease Drivers

November 2024

Driving scientific breakthroughs into powerful precision medicine

Groundbreaking Science

Targeting validated genetic disease **mis-splicing targets** in neurodegeneration and beyond

Next-gen precision medicines developed through **relevant human disease models**

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

First & Best-in-Class Programs

Three programs in the clinic with disease-relevant biomarker readouts in 2025

Proprietary FlexASO™ platform to enable additional therapies

Most programs may benefit from **Orphan Drug and Breakthrough designations**

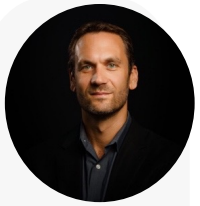
World-Class Team to Execute

Experienced executive team

Validation through partnership with Lilly, substantiates our approach and platform

$143.5M equity raised, along with Lilly partnership upfront

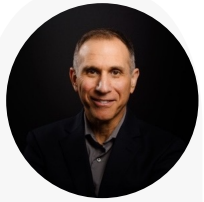
Pioneers with unrelenting commitment to patients



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

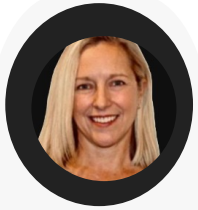
Hagen Cramer, PhD
CTO

Avecia

Girindus
Solvay Organics

Ridgeway Biosystems Inc.

WAVE LIFE SCIENCES



Robin Wojciezek, PharmD
Head of Regulatory Affairs & Drug Safety

Lilly

FibroGen

Pfizer

Lundbeck

FDA

Doug Williamson, MD
CMO

Lilly

parexel

Lundbeck

Emma Bowden, PhD
Head of Clinical Development

Lilly

Sangamo THERAPEUTICS

ThermoFisher SCIENTIFIC

AstraZeneca
MedImmune

Jason Brown, MBA
CFO

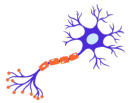
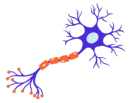
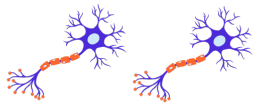
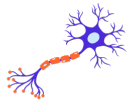
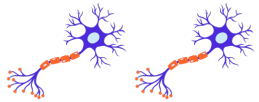
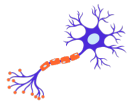
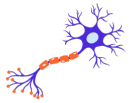
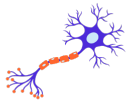
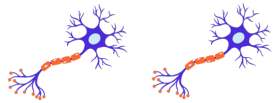
KARUNA THERAPEUTICS

PURETECH
GIVING LIFE TO SCIENCE

NOVARTIS

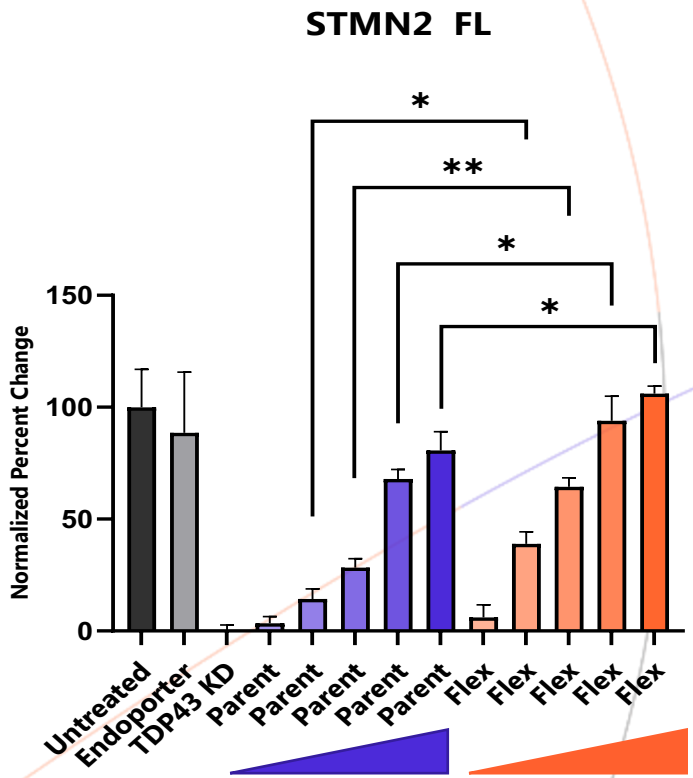
Flex ASO™ is the leading splice modulation platform to restore proteins

Flex ASO™ is a proprietary anti-sense oligonucleotide 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 stat. sig. increase in protein restoration vs. parent



Genetic validation of targets provides unprecedented opportunities

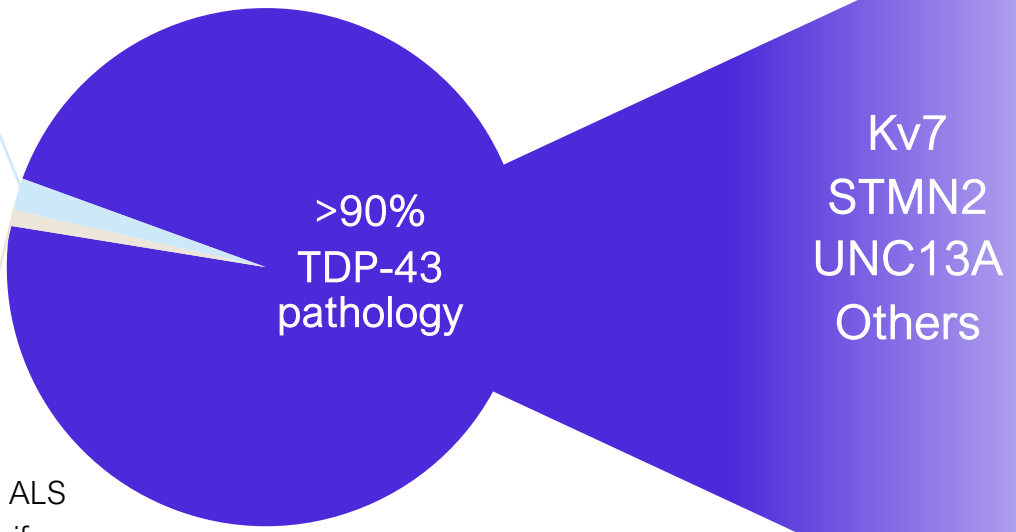
Therapeutic interventions for genetic targets for familial population have been validated

QurAlis is targeting TDP43-associated ALS using precision-medicine approaches in sporadic population

2% SOD1 ALS

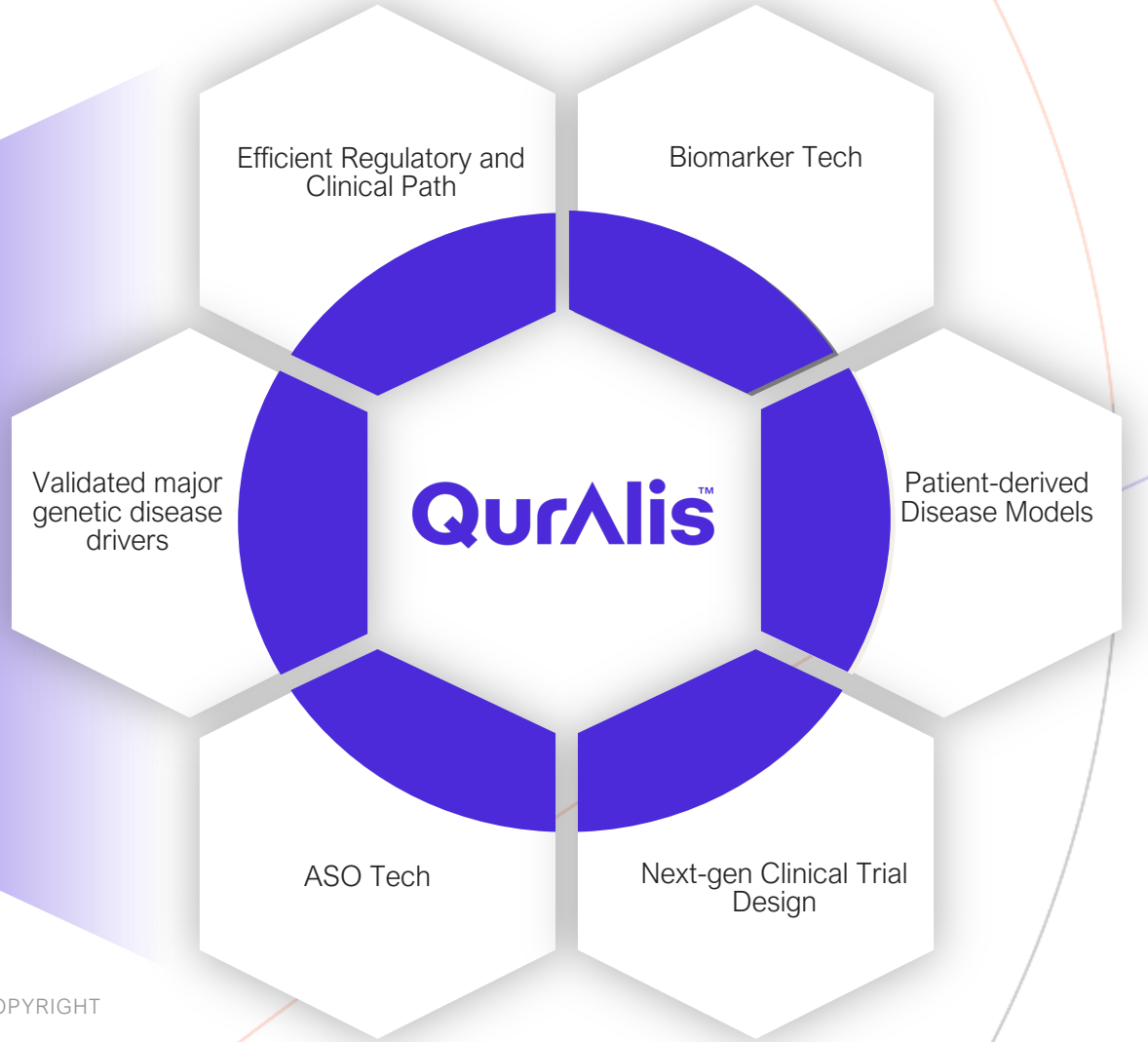
QALSODY (tofersen) 100 mg/1.5 mL injection

Approved 2023*



1% FUS ALS
ION363/jacifusen
in Phase 3**

Kv7
STMN2
UNC13A
Others



*Biogen. (2023). *Qalsody (tofersen) [package insert]*. Retrieved from https://www.biogen.com

**"Jacifusen (ION363) - Investigational Antisense Therapy for FUS-ALS." *Ionis Pharmaceuticals*, 2024. Available at Ionis Pharmaceuticals.

QurAlis' rich, diversified pipeline across CNS disorders

TARGETING MAJOR DISEASE DRIVERS IN PATIENTS

PROGRAM	DISEASE MECHANISM	MODALITY	MOA	INDICATION	PRECLINICAL	CLINICAL	PARTNER
QRL – 101	Splicing/ Excitotoxicity	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	Fragile-X			
QRL – TBA				PSP			

- Disease modifying first-in-class programs for five high profile rare disease genetic splicing targets
- Portfolio expansion beyond ALS, to other rare and large indications creating additional growth opportunities
- FlexASO™ platform, validated by Lilly, provides unique opportunities for splice modulation 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 ASO candidates in Phase 1 (1) and FIH-enabling studies (2)
- 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

Supported and recognized by investors, pharma, and industry

Investors

EQT Life Sciences
sanofi ventures
DROIA ventures
LS POLARIS INNOVATION FUND
Lilly
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 AWARDS WINNER

THE TERMEER FOUNDATION

Partner

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, epilepsy and mood disorders, marketed for partial-onset seizures, but ultimately being withdrawn (2017) for undesirable side effect profile limiting commercial potential
  - Ezogabine also demonstrated signal of disease modification in proof of mechanism 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 BHV7000 in epilepsy studies

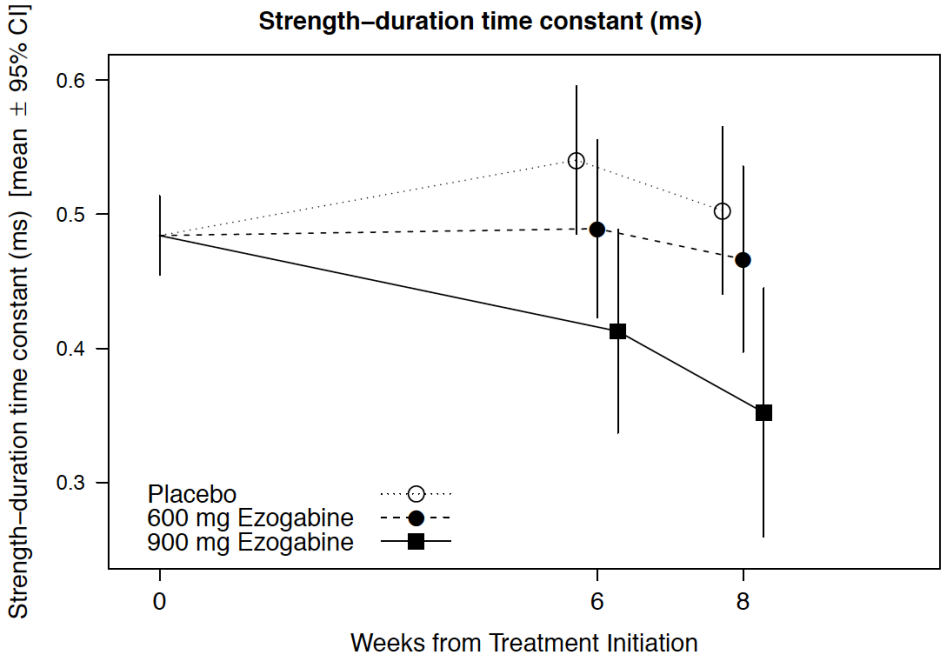
- QurAlis is developing QRL-101, a highly selective Kv7.2/3 channel opener in proof of mechanism studies ALS and epilepsy to inform dosing & indication selection for Phase 2
  - High affinity to Kv7.2/3
  - Lack of affinity to $GABA_A$ receptors and other Kv7 subtypes

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

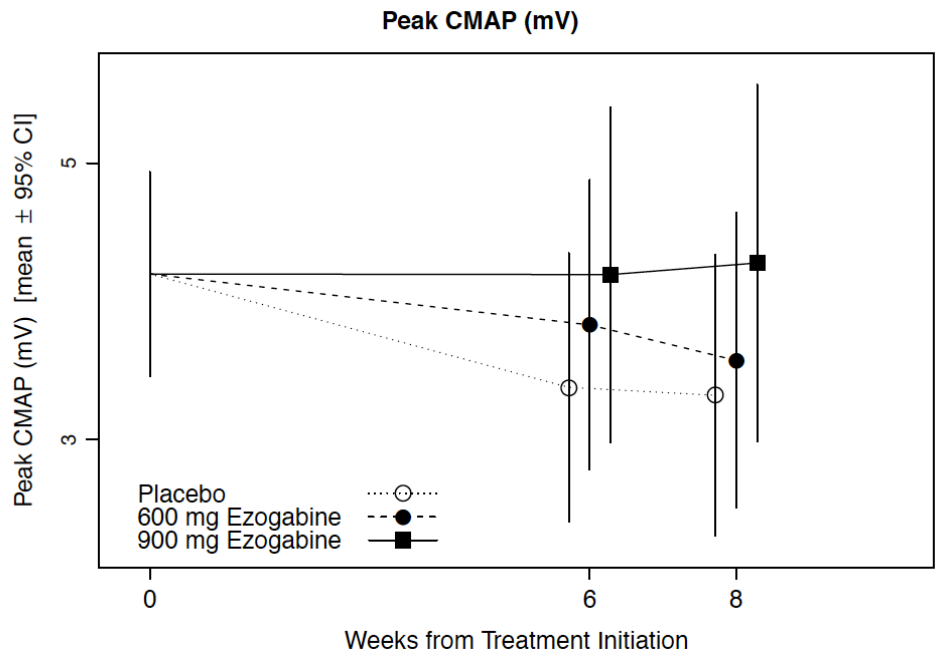
Kv7 is a clinically validated target in ALS

65 patient Ezogabine published trial results validated the importance of reducing hyperexcitability through Kv7

Significant, Dose Dependent Effects on Biomarkers That Predict Patient Survival



Significant Correlation Between Effect Size on Excitability Biomarker and Efficacy Biomarker CMAP

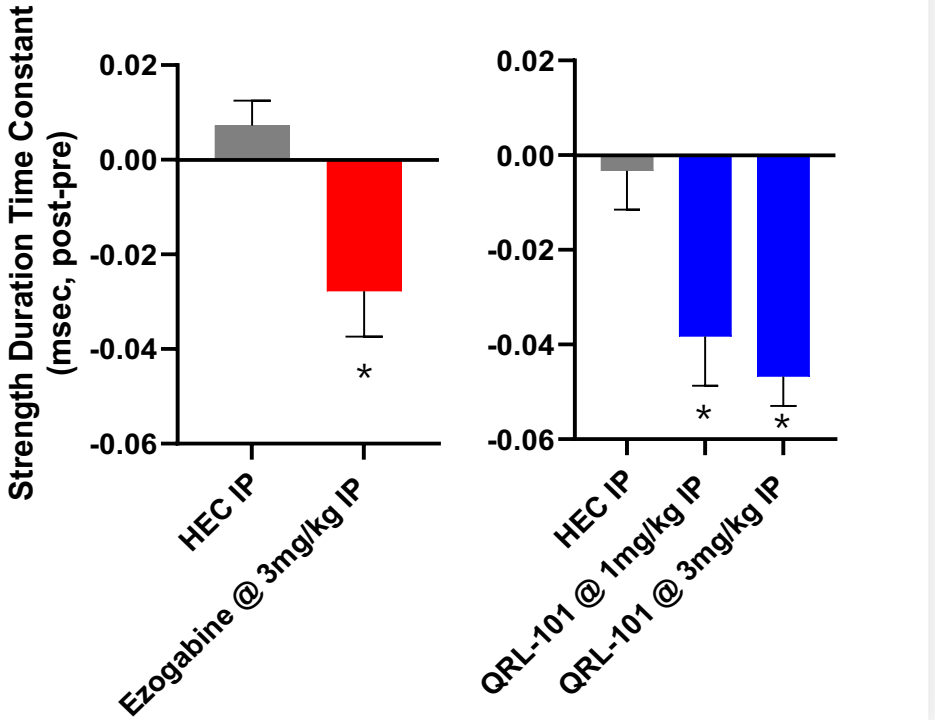


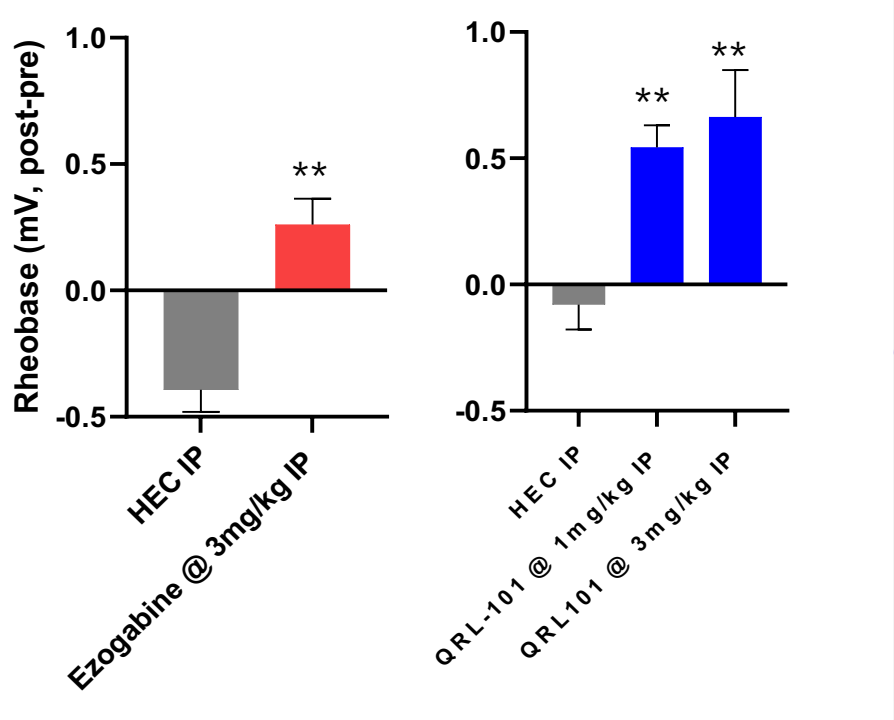
Nearly all (97%) participants in the trial reported at least one adverse event.
The most frequent adverse events among participants given Ezogabine were fatigue and dizziness

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

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

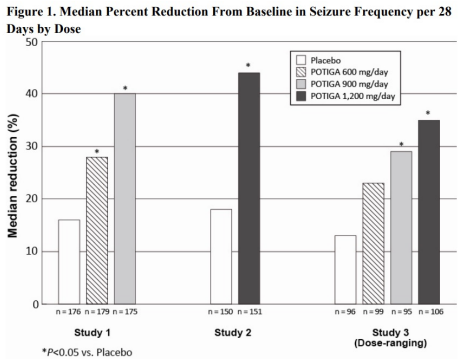




Kv7 compounds have consistently demonstrated anti-seizure activity

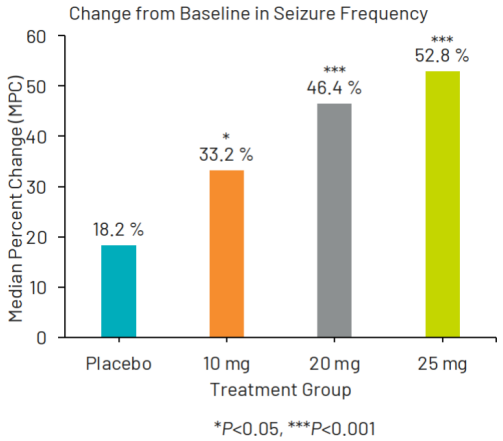
Evolution has focused on increased Kv7.2/3 specificity to decrease off-target side effects

Ezogabine (POTIGA)



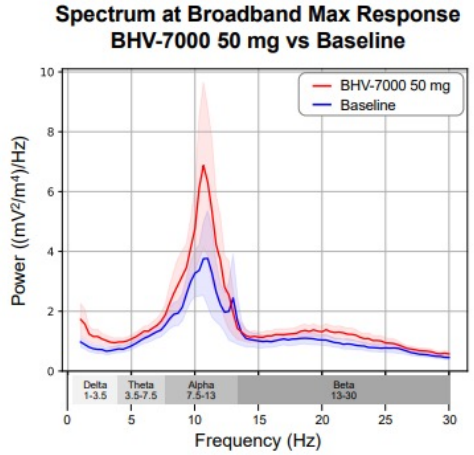
- Pivotal studies demonstrated dose-dependent improvement in baseline seizure frequency in partial-onset seizures
- 1,200mg dose associated with 32% dizziness, 27% somnolence
- Blue-grey skin discoloration observed in post-approval adverse effects reporting
- GSK discontinued marketing ezogabine in 2017

Azetukalner (XEN1101)



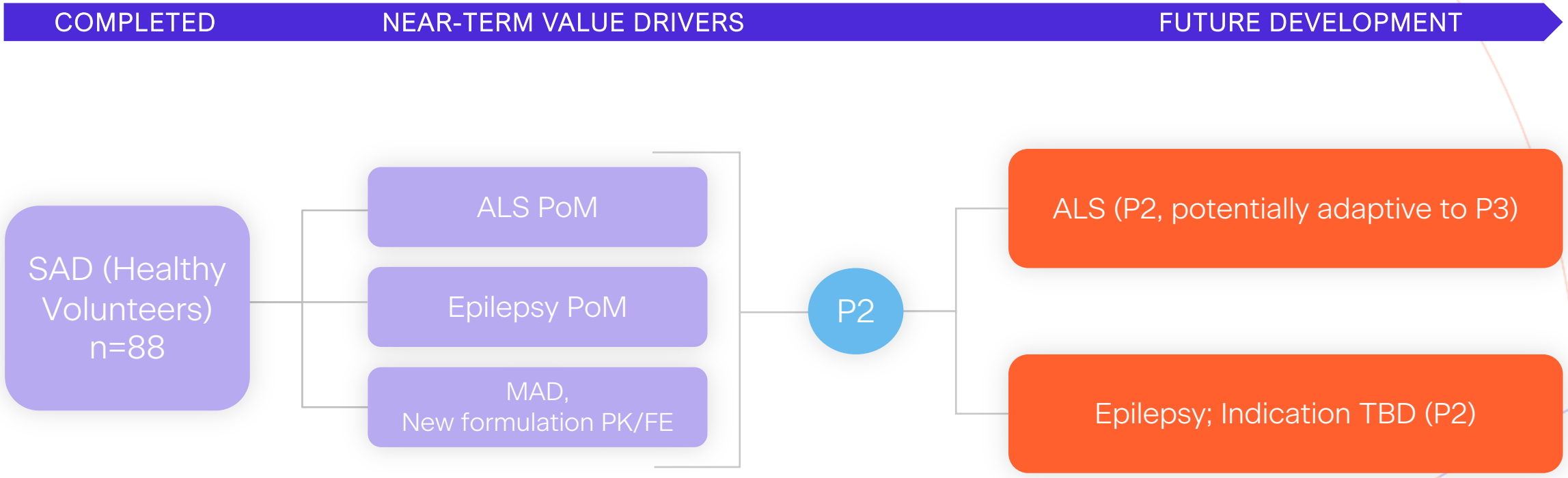
- Phase 2 X-TOLE study demonstrated dose-dependent improvement in baseline seizure frequency in focal-onset seizures
- AEs of dizziness (24.6%) and somnolence (15.6%) reduced relative to ezogabine in X-TOLE study; no new AEs identified in OLE
- Currently enrolling two Phase 3 studies

BHV-7000



- Phase 1 MAD data demonstrated improved AEs of dizziness (10%) and somnolence (0%)
- Phase 1 single dose open-label EEG study in 11 healthy volunteers demonstrated dose-dependent increases in spectral power
- Currently enrolling two Phase 2/3 studies in Focal-Onset Seizures (FOS), one Phase 2/3 study in Idiopathic Generalized Epilepsy (IGE)

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 Proof of Mechanism (PoM) Design

- Single-dose placebo-controlled design at three ascending dose levels
- 12 patients (4 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 Proof of Mechanism (PoM) Design

- 3-way crossover design (placebo, low dose, high dose)
- 28 healthy volunteers all receive each treatment
- 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; resting motor threshold, peak to peak amplitude, motor evoked potential
- Pharmaco-electroencephalography (pEEG) endpoints; changes in passive EEG

Topline data for both studies are expected H1 2025

RNA Recovery

QRL-201 protects human motor neurons against neurodegeneration through restoration of STMN2

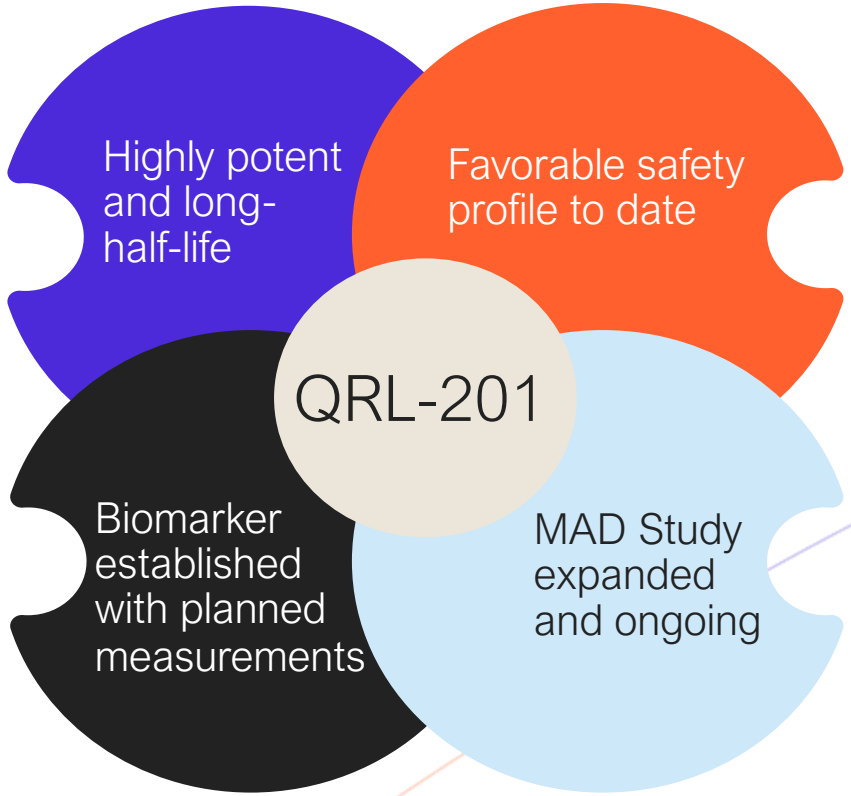
First-in-class therapy to treat
~90% of ALS & ~50% FTD patients

Genetic target for sporadic ALS
and FTD with additional opportunities in AD and PD

Potent restoration of STMN2 function and TDP-43 neurodegenerative phenotypes in human motor neurons

Comprehensive biomarker program combined with clinical readouts maximizes probability of success

QurAlis retains global rights, CoM patent through 2039 plus potential PTE, pending issuance



Therapeutic rationale STMN2 protein restoration by ASO

- STMN2 is the most consistently downregulated gene in sporadic ALS patients; this is caused by mis-splicing of STMN2 pre-mRNA
- Downregulation and loss of STMN2 alone in mice leads to loss of muscle innervation, motor neuron axonopathy and muscle atrophy, all hallmarks of ALS
- Restoration of STMN2 through ASO treatment restores neuronal processes, Golgi outposts and protects neuronal activity in human motor neurons with TDP-43 pathology
- Two approved ASO therapies for motor neuron diseases (Spinraza® for SMA and QalSody® for ALS) show that an ASO therapy strategy to restore STMN2 in ALS patients is technologically de-risked
- Biomarker studies in mice suggest that the functional impact of STMN2 restoration on muscle innervation can be measured with electrophysiological biomarkers (CMAP) in the clinic supporting a precision clinical development strategy

STMN2 levels are consistently decreased in sporadic ALS

BREAKTHROUGH DISCOVERY VALIDATED SIMULTANEOUSLY

EGGAN LAB[1]

STMN2 levels are consistently decreased in sporadic ALS patients

Truncated STMN2 mRNA abundant in sporadic ALS spinal cord and brain

CLEVELAND LAB[2]

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

TDP-43 loss causes loss of axon repair Rescue by restoring STMN2 levels

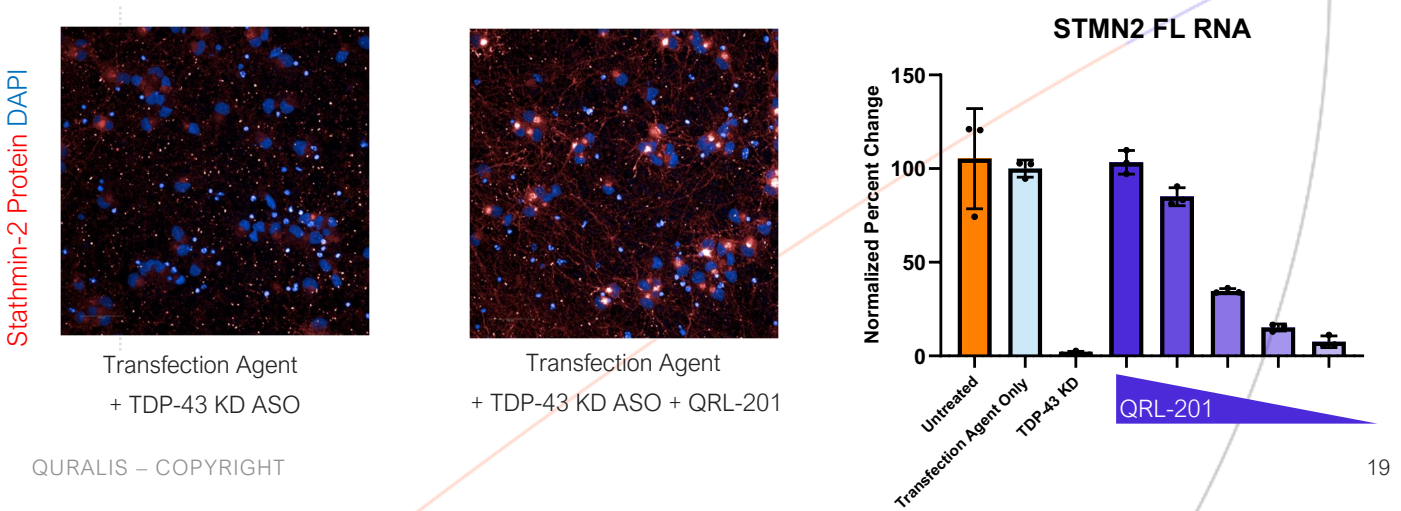
QURALIS' THERAPEUTIC STRATEGY FOR STMN2 RESTORATION

In ALS motor neurons TDP-43 leaves the nucleus

Loss of TDP-43 controlled splicing leads to loss of STMN2

Loss of full length STMN2 leads to axonal degeneration and damaged repair

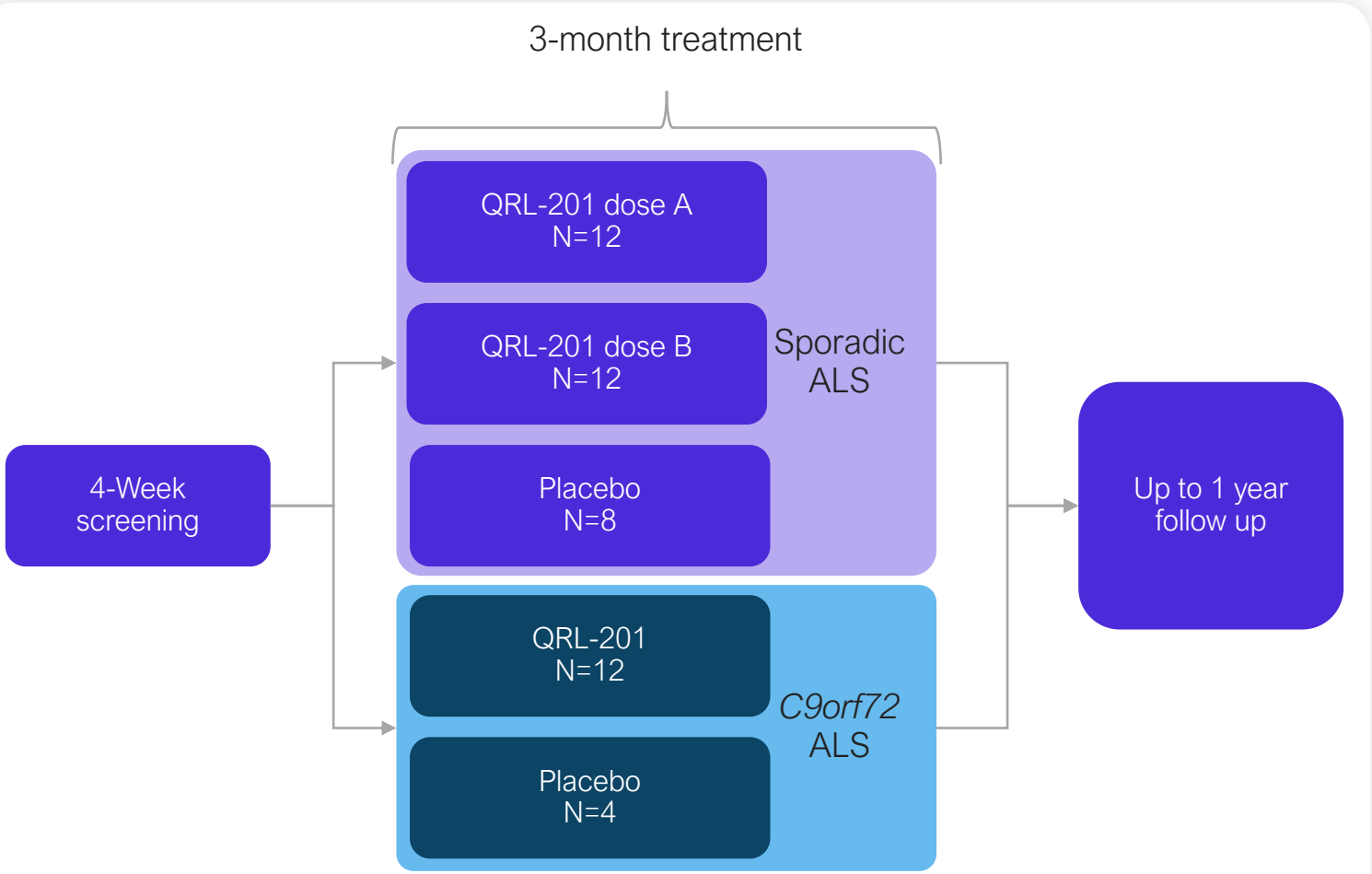
QRL-201 RESTORES LEVELS OF FULL-LENGTH STMN2



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

ANQUR study redesign optimized for dose range finding & signal detection

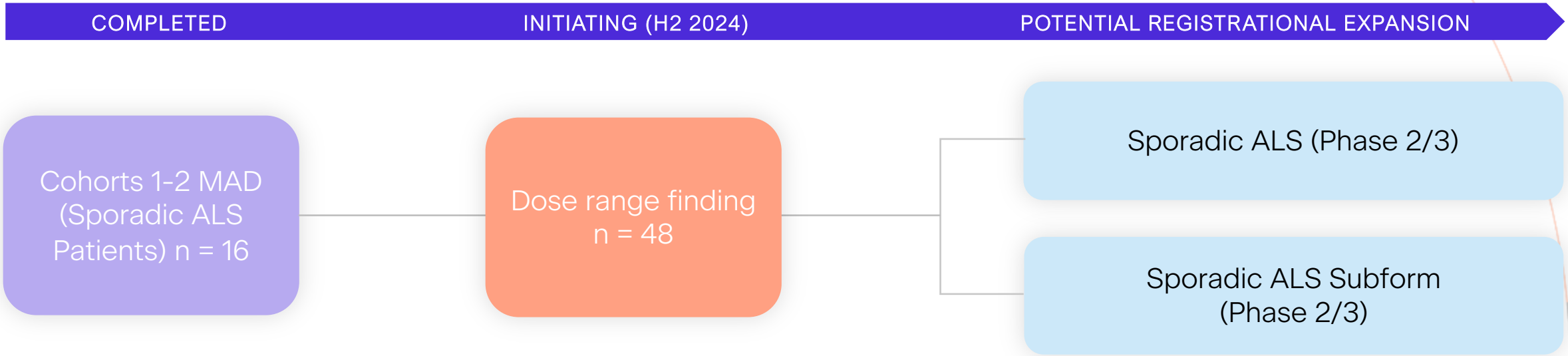
Enrollment to re-start in H2 2024, 12-month data[1] expected H1 2026



[1]3-months dosing and 9-months post-dosing follow-up

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

QRL-201 clinical development plan: ANQUR study



Key Biomarkers

- CMAP (e-phys)
- NfL
- Target engagement

ANQUR data will guide…

- Potential for expanding Ph1 protocol into Phase 2/3 adaptive design studies
- Potential to seek FDA EOP2 feedback

[1]8 Sporadic ALS and 4 C9orf72 ALS

Driving scientific breakthroughs into powerful precision medicine

Groundbreaking Science

Targeting validated genetic disease **mis-splicing targets** in neurodegeneration and beyond

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Proprietary FlexASO™ platform to enable additional therapies

Most programs may benefit from **Orphan Drug and Breakthrough designations**

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Experienced executive team

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Thank You

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