ANQUR, the First-in-Human Phase 1 study of QRL-201 in ALS Advances to Dose-Range Finding using a Novel Population Pharmacokinetic Analysis

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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 3 to 5 years, and approximately 10% of ALS patients survive for longer than 10 years. There is no cure for ALS, and the currently approved therapies provide only modest benefit for people living with ALS.
- A hallmark of ALS, seen in postmortem tissue from 90% to 95% of all patients, is a loss of nuclear TAR DNA Binding Protein 43 (TDP-43) and the presence of cytoplasmic aggregates.
- Stathmin-2 (STMN2) is the most consistently decreased gene across multiple ALS RNA expression studies. Loss of nuclear TDP-43 leads to STMN2 mis-splicing, resulting in loss of full-length transcript and protein. Our therapeutic approach is to restore STMN2 protein by correcting the mis-splicing of the pre-mRNA.
- QurAlis has developed an investigational splice switching antisense oligonucleotide (ASO), QRL-201, for the recovery of STMN2 expression and function in ALS patients, even in the continued presence of TDP-43 pathology.

METHODS

- Given the rapid progression, life-threatening, and rare nature of ALS, as well as the high unmet medical need, QurAlis designed a first in human study evaluating the safety and tolerability of multiple doses of QRL-201 in people living with ALS.
- QRL-201-01 (also known as the ANQUR study) is a multi-center, randomized, double-blind, placebo-controlled, multiple-ascending dose (MAD), Phase 1 study in which approximately 64 people living with ALS will receive QRL-201, or matching placebo, in a 6:2 ratio.

STUDY OBJECTIVES & ENDPOINTS

Primary Objective & Endpoint	Secondary Objective & Endpoint
➢Determine safety and tolerability of QRL-201 • Treatment emergent adverse events (TEAEs), Serious Adverse Events (SAEs), and other non-serious Adverse Events (AEs)	➢Determine the plasma PK profile of QRL-201 after multiple doses • Multiple dose PK (systemic exposure): C_{max}, AUC, and T_{max}

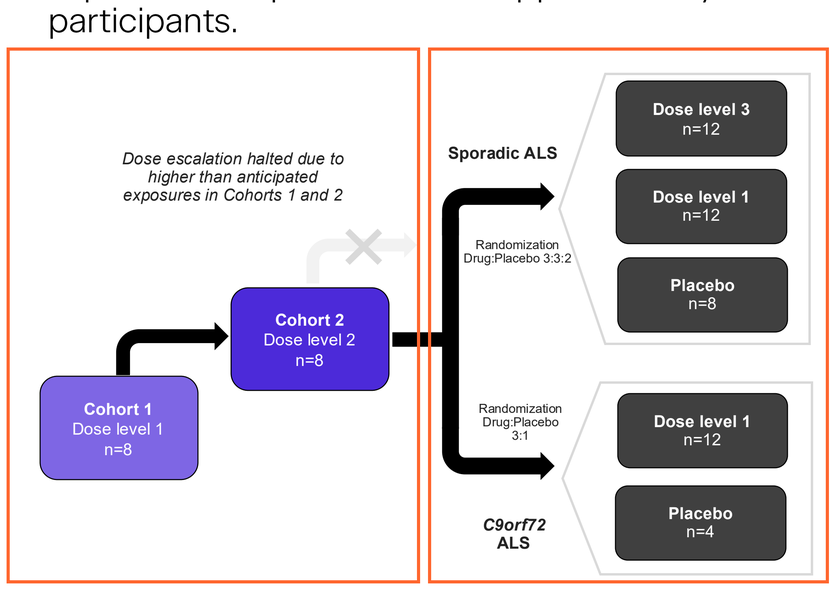
Exploratory Objective & Endpoints: biomarkers	Exploratory Objective & Endpoints: clinical outcomes	Exploratory Objective & Endpoints: PK
➢Determine the effects of QRL-201 on biomarkers of neuronal loss and STMN2 biology • Neurofilament levels • STMN2 protein levels • CSF CHIT3L1 • Plasma pTau	➢Determine the effects of QRL-201 on clinical assessments • ALSFRS-R • ROADS • King's Staging • Slow vital capacity (SVC) • Muscle strength • Electrophysiology markers of denervation	➢Determine the CSF PK profile of QRL-201 after multiple doses • Multiple dose CSF PK

INVESTIGATIONAL PRODUCT

QRL-201	• Splice switching ASO against STMN2 pathology
Function/MoA	• Correct *STMN2* mis-splicing & restoration of STMN2 protein
Route of Administration	• Intrathecal injection
Dosing Regimen	• Multiple ascending doses of QRL-201
Placebo	• Supplied; artificial CSF • Same route of administration and regimen as QRL-201

STUDY DESIGN

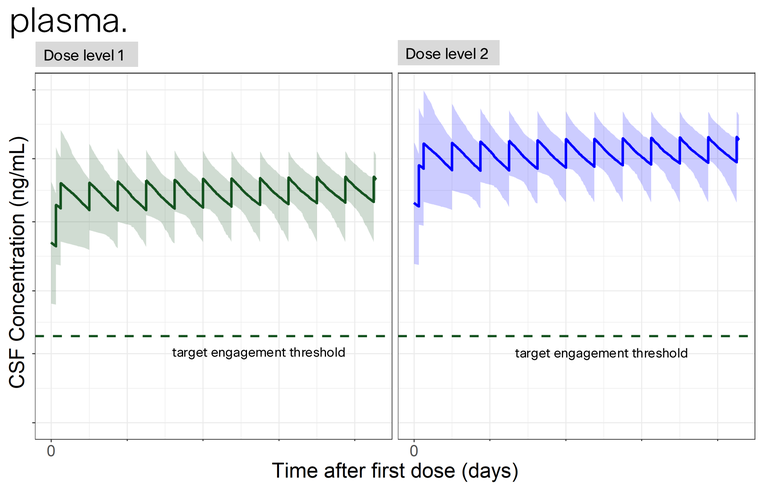
- Informed by recent human PK results (described under "Clinical PK Model"), the current study design includes two dose escalation cohorts (of 8 participants each), followed by a dose exploration phase of approximately 48 participants.



N = 64
All cohorts randomized 6:2 (QRL-201 : placebo)
Replacement participants at QurAlis' discretion

CLINICAL PK MODEL

- A model to determine the approximate half-life of QRL-201 in humans was developed using plasma and cerebrospinal fluid (CSF) data from 12 patients from Cohorts 1 and 2. Results demonstrated a half-life in CSF of approximately 100 days. The model was used to predict half-life exposures at additional dose levels within the ANQUR study, as well as putative chronic dose regimens. Compared with the clinical dataset, this model consistently captures the concentration of QRL-201 both in the CSF and in plasma.



KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- Male or female participants aged 18 to 80 years diagnosed with ALS
- ALS symptom onset within 24 months of screening
- Slow vital capacity >50%
- Clinical and electrophysiologic evidence of lower motor neuron involvement
- Not pregnant and not nursing
- Willing and able to practice effective contraception
- Able to tolerate lumbar puncture
- If on approved therapies for the treatment of ALS during the course of the study, must be on a stable dose (at the Sponsor's discretion)

Exclusion Criteria

- Pathogenic variant, likely pathogenic variant, or variant of uncertain significance in the superoxide dismutase 1 (SOD1) and/or fused in sarcoma (FUS) genes
- Currently enrolled in any other clinical study involving either an investigational product (IP) or off-label use of a drug or device
- Prior exposure to stem cell or gene therapy products
- Any contraindication to intrathecal drug administration
- Abnormal laboratory values deemed clinically significant by the Investigator
- Significant infection, or known inflammatory process

CONCLUSIONS

- The ANQUR study has received regulatory authorization in Canada, the United Kingdom, and in the European Union. Recruitment in the dose exploration phase of the study is ongoing.
- QurAlis' mission is to bring breakthrough precision medicine technology to people living with ALS. QRL-201-01 is designed to evaluate the safety and tolerability of multiple doses of QRL-201 in people living with ALS and explore the hypothesis that restoration of STMN2 is a suitable disease modifying approach in ALS.
- QRL-201 is an investigational ASO for the recovery of STMN2 expression and function in ALS patients, even in the continued presence of TDP-43 pathology.
- To investigate QRL-201, QurAlis has designed a first in human study evaluating the safety and tolerability of multiple doses of QRL-201 in people living with ALS.
- 64 study participants planned, at up to 16 sites. Sporadic ALS enrollment has completed, but is still on-going for C9orf72. Visit www.clinicaltrials.gov for further details and updates: NCT05633459

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