A Phase 1, Multicenter, Randomized, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Safety and Tolerability of AMX0114 in ALS (LUMINA)

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ABSTRACT #094

Background

Calpain-2

Calpain-2 is a critical effector of axonal degeneration, a key early contributor to the pathogenesis of ALS, and is known to cleave cytoskeletal proteins, including neurofilament light chain (NfL)[1-3]

AMX0114

AMX0114 is an antisense oligonucleotide inhibitor of calpain-2 (encoded by the *CAPN2* gene)[4]

Preclinical

Dose-dependent improvements in neuronal survival and reductions in NfL have been observed with AMX0114 in preclinical studies

Toxicology

AMX0114 was well-tolerated and showed no mutagenicity, genotoxicity, or cardiotoxicity in single- and repeat-dose toxicology studies in both rats and non-human primates

Objective

- The phase 1 LUMINA study will assess the safety, tolerability, PK, and PD of AMX0114 in people living with ALS

Study Design

- LUMINA is a phase 1, multicenter, randomized, placebo-controlled multiple ascending dose study in ~48 adult participants with ALS with sites in Canada and the United States
- Four dose levels of study drug (AMX0114 or placebo) are planned to be examined sequentially
- After study completion, an open-label extension study of AMX0114 may be implemented if data support a positive benefit-risk profile based on review of safety, tolerability, PK, and PD findings

Key Trial Entry Criteria

- ✓Age ≥18 years
- ✓Diagnosis of clinically definite or clinically probable ALS, based on El Escorial criteria
- ✓Time since onset of first symptom of ALS <24 months
- ✓SVC ≥ 75%
- ✓Approved treatments for ALS allowed if using stable dose for ≥30 days prior to baseline visit

Endpoints

Primary Endpoints

- Incidence of AEs, serious AEs, and dose-limiting toxicities
- Incidence of abnormalities in clinical laboratory assessments, vital signs, physical and neurological examinations, and electrocardiograms

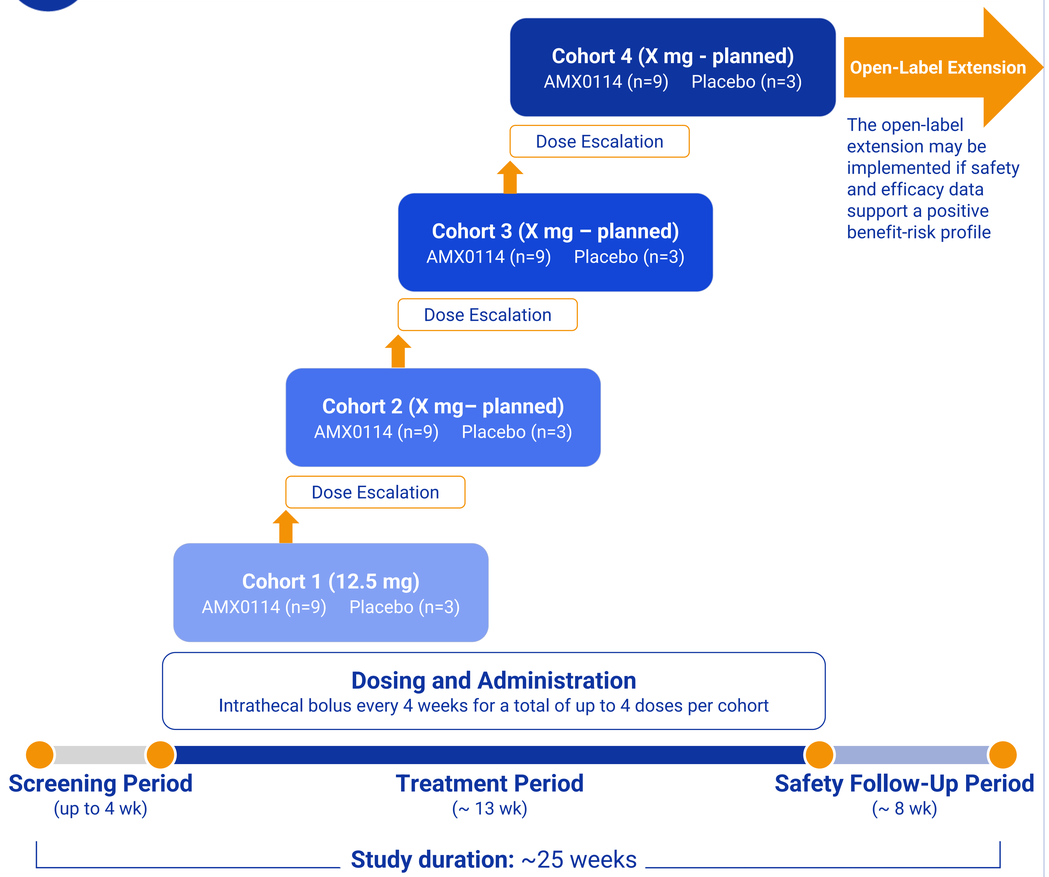
Secondary Endpoints

- PK concentrations, including plasma and CSF levels of AMX0114

Tertiary Endpoints

- Change from baseline of plasma and CSF pharmacodynamic measures of ALS and markers of target engagement (e.g., NfL, SBDP-145)
- Change from baseline of ALS Functional Rating Scale – Revised (ALSFRS-R) and SVC

LUMINA Multiple Ascending Dose Study Design



Conclusion

- AMX0114 is an ASO inhibitor of calpain-2 (encoded by the *CAPN2* gene), a critical effector of axonal degeneration
- AMX0114 has shown benefit on neuronal survival and reduction of neurofilament light chain across multiple disease-relevant cell types and preclinical models
- LUMINA is a first-in-human, multiple ascending dose study evaluating the safety, tolerability, PK, and PD of AMX0114 in adults with ALS
- Sites are activated in Canada and the U.S., and the first participant was dosed in April 2025. Amylyx is working to open remaining sites for screening, enrollment, and dosing.

References

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Abbreviations:

AE, adverse event; CSF, cerebrospinal fluid; NfL, neurofilament light chain; PD, pharmacodynamics; PK, pharmacokinetics; SBDP-145, spectrin breakdown product 145; SVC, Slow vital capacity.

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