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

*Lauren Kett,[1] Sabrina Paganoni,[2,3] Jeremy Shefner,[4,5] Leonard van den Berg,[6] Lauren Kingston,[1] Evan Mizerak,[1] John Pesko,[1] Lahar Mehta,[1]*

[1]Amylyx Pharmaceuticals, Inc., Cambridge, Massachusetts, USA; [2]Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [3]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts, USA; [4]Barrow Neurological Institute, Phoenix, Arizona, USA; [5]Creighton University College of Medicine, Phoenix, Arizona, USA; [6]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT #146

## 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 NfL[1-3]

### AMX0114

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

### Pre-Clinical

Dose-dependent improvements in neuronal survival and reductions in neurofilament light chain 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, pharmacokinetics (PK), and pharmacodynamics (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
- 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 will 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
- ✓ Slow vital capacity (SVC) ≥ 75%
- ✓ Approved treatments for ALS are allowed if participant is on a stable dose for at least 30 days prior to baseline visit

### Endpoints

**Primary Endpoints**

- Incidence of adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities (DLTs)
- Incidence of abnormalities in clinical laboratory assessments, vital signs, physical and neurological examinations, and electrocardiograms

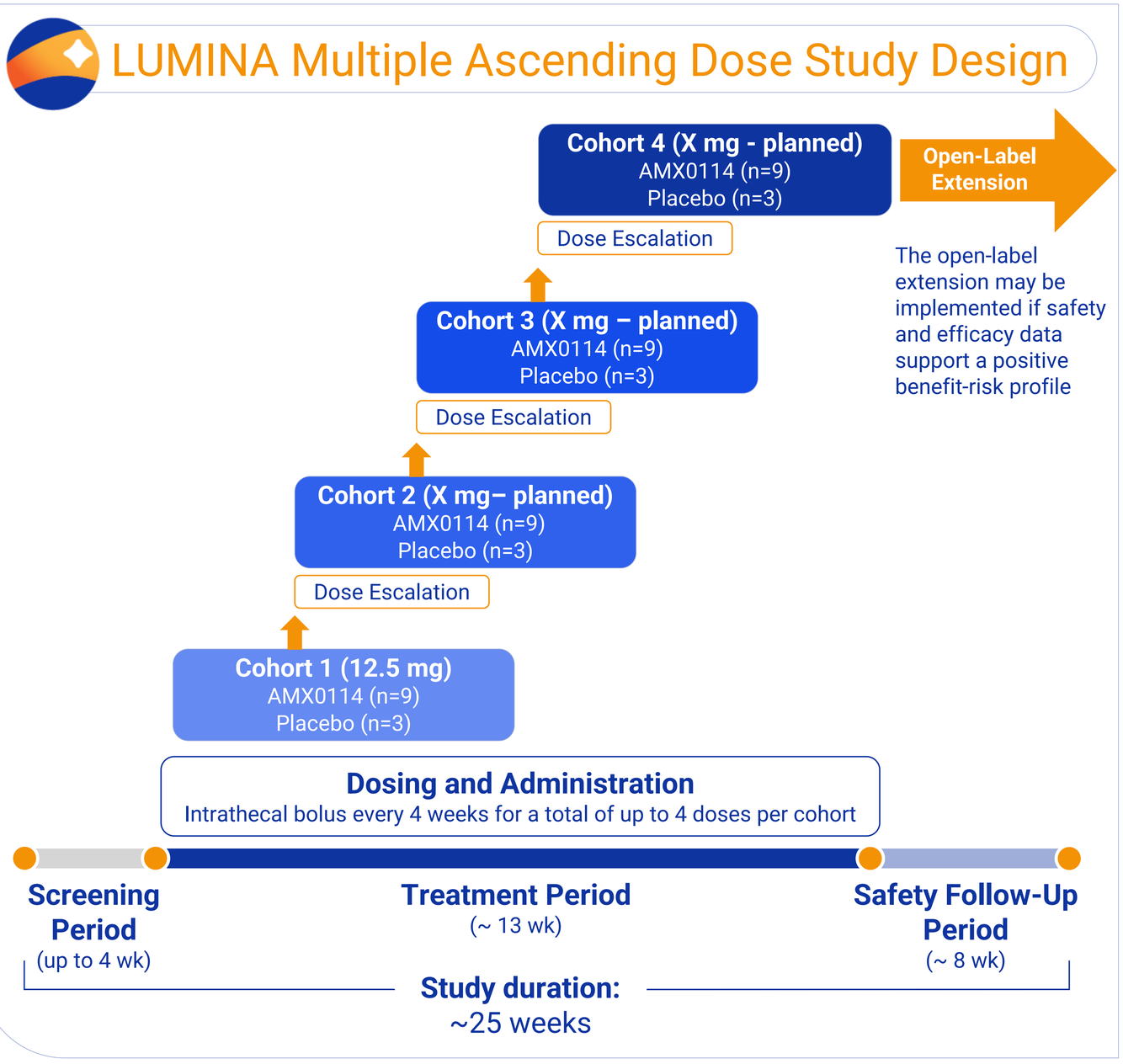
**Secondary Endpoints**

- PK concentrations, including plasma and cerebrospinal fluid (CSF) levels of AMX0114

**Tertiary Endpoints**

- Change from baseline of plasma and CSF pharmacodynamic measures of ALS and markers of target engagement (e.g., calpain-2 levels, NfL, SBDP-145)
- Change from baseline of ALS Functional Rating Scale – Revised (ALSFRS-R) and slow vital capacity (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 pre-clinical models
- LUMINA is a first-in-human, multiple ascending dose study evaluating the safety, tolerability, PK, and PD of AMX0114 in adults with ALS

**References**

1. Suzuki N, et al. *Front Neurosci*. 2020;14:194. 2. Ma M. *Neurobiol Dis*. 2013;60:61-79. 3. Asakawa K, et al. *Cell Mol Life Sci*. 2021;78(10):4453-4465. 4. Cohen J et al. Presented at 2024 MDA Clinical and Scientific Conference; March 3-6, 2024; Orlando, Florida.

**Abbreviations:**

NfL, neurofilament light chain; SBDP-145, spectrin breakdown product 145.

**Disclosures**

**SP** reports research grants from Amylyx Therapeutics, Revalesio Corporation, Eledon, Alector, UCB Pharma, Biohaven, Clene Nanomedicine, Prilenia Therapeutics, Seelos, Calico, Denali, NIH, CDC, DoD, the ALS Association, the Muscular Dystrophy Association, Tambourine and reports consulting fees from Amylyx, Arrowhead, BMS, Clene, Iris, Eikonizo, and Cytokinetics. She has been a paid educational speaker for PeerView and Medscape. **JS** reports research funding from Amylyx, Biogen, Cytokinetics Incorporated, Ionis, Mitsubishi Tanabe Pharma America, Quralis, PTC, Sanofi, Wave, and Myolex. He reports personal compensation for consulting from Amylyx, Cytokinetics, Denali, GSK, Mitsubishi Tanabe Pharma America, Neurosense, Orthogonal, Pinteon, RRD, Acurastem, Revalasio, Apellis, Swanbio, Novartis, Sanofi, Eikonizo, and Sarepta. **LvdB** reports consulting fees from Amylyx, Argenx, Cytokinetics, Denali, Projenx, Sanofi, Takeda, and Verge. **LK, LK, EM, JP** and **LM** are full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.

**Acknowledgements**

The authors would like to thank the ALS clinicians as well as people living with ALS and their caregivers for providing feedback and advice on the study design.

This study is sponsored by Amylyx Pharmaceuticals, Inc.

**Presented at NEALS Virtual Meeting 2024; October 21-24, 2024**