LUMINA Study Update

Lauren Kett, MD, PhD
Senior Medical Director
Amylyx Pharmaceuticals

Sabrina Paganoni, MD, PhD
Co-Director, Neurological Clinical Research Institute,
Sean M. Healey & AMG Center for ALS at MGH

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

Please Note

- AMX0114 is an investigational drug and has not been approved by any health authority.

- This presentation is intended to provide scientific information about AMX0114. The statements and content shared in this presentation have not been evaluated by any health authority.

Disclosures

LK is a full-time employee of and may have stock option ownership in Amylyx Pharmaceuticals, Inc. **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.

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

Presentation Overview

Modulating Neurodegeneration in ALS: Calpain-2 and AMX0114

- Role of Calpain-2 in Axonal Degeneration and ALS
- About AMX0114
- AMX0114 Preclinical Data
- Elucidating the Biomarker Signature of Calpain-2 Activation

LUMINA Study Design

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX

Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

Modulating Neurodegeneration in ALS: Calpain-2 and AMX0114

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX®

Calpain-2 is a Ca^{2+}-Activated Cysteine Protease that Drives Axonal Degeneration and Has Been Implicated in the Pathogenesis of ALS[1-6]

Rationale for Targeting Calpain-2 in ALS

- **Calpain-2 levels are upregulated in ALS[4,6]**
  - *CAPN2* mRNA upregulated in biopsied muscle samples of people with ALS[4]
  - Ratio of active to inactive calpain-2 in post-mortem spinal cord tissue of people with ALS ~3x higher than that in healthy controls[6]

- **Calpain-2 inhibition has demonstrated benefit in ALS mouse model[5]**
  - Neuron-specific overexpression of calpain inhibitor calpastatin increased overall survival and delayed disease onset in ALS SOD1G93A mouse model[5]

1. Moloney EB, et al. Front Neurosci. 2014;8:252. **2.** Ma M. Neurobiol Dis. 2013;60:61-79. **3.** Asakawa K, et al. Cell Mol Life Sci. 2021;78(10):4453-4465.
4. Ueyama H et al. *J Neurol Sci.* 1998;155():163-169. **5.** Rao MV et al. *J Neurochem.* 2016;137(2):253-265. **6.** Yamashita, T et al. Nat Commun. 2012; 3:1307.

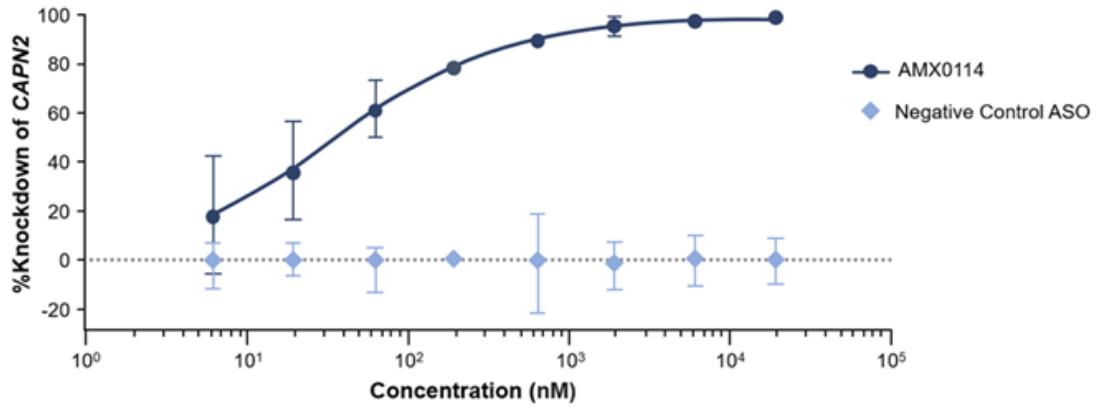
For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX

AMX0114: An Antisense Oligonucleotide (ASO) Targeting Calpain-2

Selectivity of the ASO modality of AMX0114 may offer distinct advantages over earlier, small molecule-based approaches to targeting calpain-2 including:

- Inhibition of calpain-2 without disrupting the function of other calpains or calpastatin
- Targeting of an exon in the active site of the calpain-2 protease
- Lowering of *CAPN2* mRNA levels through RNase H-mediated degradation, driving lower levels of functional calpain-2 protein



AMX0114 has been shown to achieve potent, dose-dependent, and durable knockdown of CAPN2 mRNA and calpain-2 protein in human motor neurons[1]

1. Cohen J, et al. Presented at the 22nd Annual NEALS Meeting; Clearwater Beach, Florida; October 4-6, 2023.

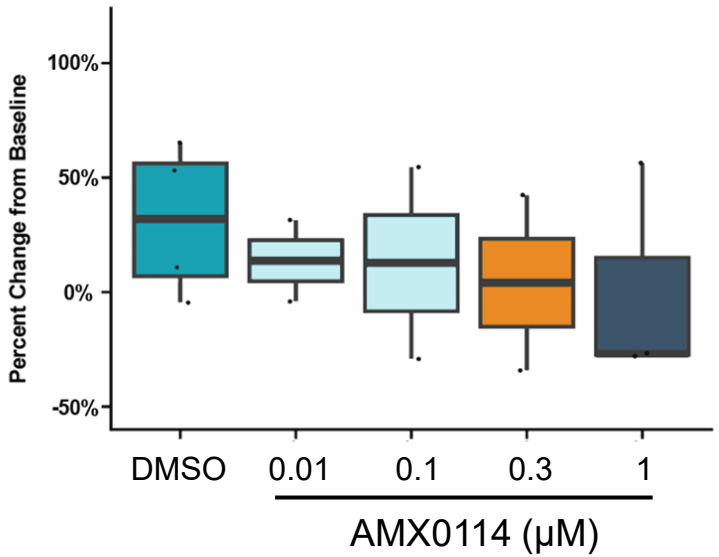
For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX

AMX0114 Has Been Shown to Reduce Extracellular NfL Levels and Improve Neuron Survival in TDP-43 ALS Models

AMX0114 Reduced Extracellular NfL[1]

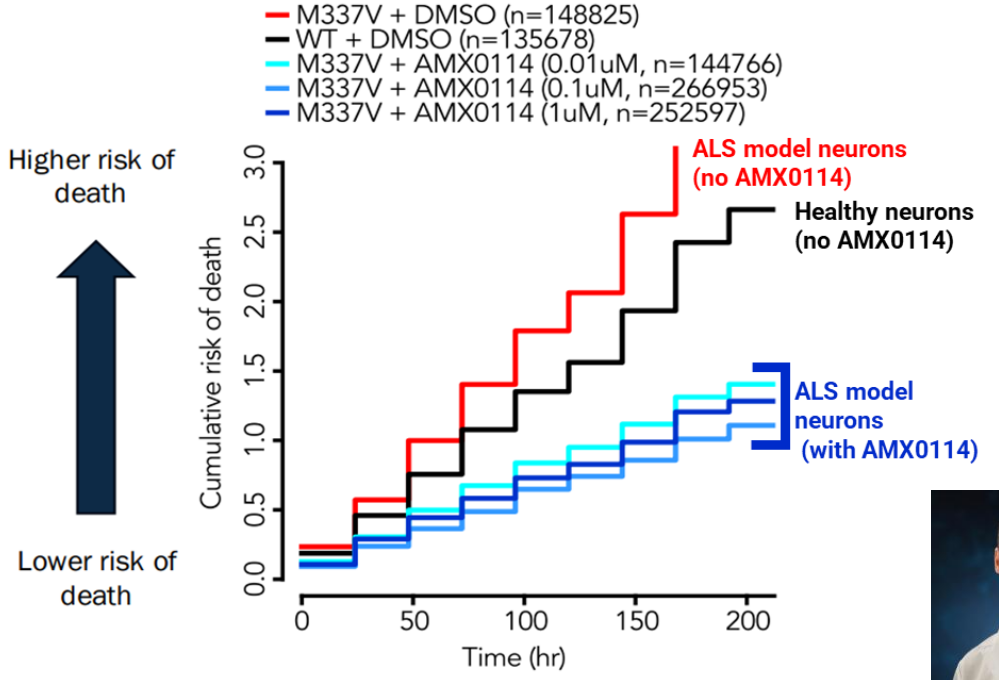
Treatment with 0.1 µM AMX0114 resulted in ~60% decrease in extracellular NfL relative to DMSO (vehicle)-treated M337V controls

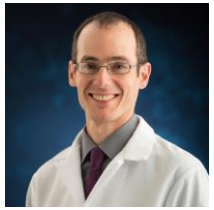


Cultures treated with a single dose of AMX0114 (0.01, 0.1, 0.3, or 1 µM) or vehicle (DMSO). Medium was harvested 10 days later and NfL levels were assessed by ELISA. "Baseline" refers to NfL levels in isogenic controls.

AMX0114 Improved Neuron Survival[1]

67.8% lower hazard ratio for TDP-43 mutant (M337V) cells treated with 0.1 µM AMX0114 vs. vehicle (DMSO)-treated M337V cells (p<0.0001)





Barmada Lab

1. Mizerak E, et al. Presented at the TIDES USA Conference; Boston, MA; May 14-17,2024.

DMSO; dimethyl sulfoxide

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX

Calpain-2 Substrates Allow for a Unique Biomarker Strategy to Evaluate AMX0114 Target Engagement + Efficacy

Calpain-2 Activation

Markers of Target Engagement

- SBDP-145 (calpain-specific breakdown product of αII-spectrin)
- NfL
- Calpain-specific NfL fragments

Axonal Degeneration

Markers of Axonal Injury

- SBDP-145
- NfL
- Calpain-specific NfL fragments
- pNFH

ALS Progression

Markers Correlating to Functional Progression and Survival

- NfL
- pNFH
- Other TBD

Calpain-2 substrates include:[1-4]

- Cytoskeletal proteins
  - αII-spectrin
  - NfL
  - Microtubule-associated proteins (tau)
- TDP-43
- Cell death pathway signaling proteins

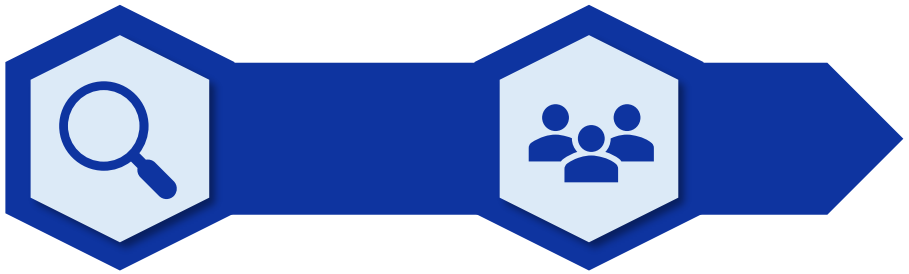
Bowser Lab

1. Ono Y, Saido TC, Sorimachi H. Nat Rev Drug Discov. 2016;15(12):854-876. **2.** Ma M, et al. Neurobiol Dis. 2013;56:34-46. **3.** Yamashita, T et al. Nat Commun. 2012; 3:1307. **4.** Wang Y, et al. Cells.2020;9(12):2698.

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX

LUMINA Study Design & Updates



For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

LUMINA Is a Phase 1, Multicenter, Randomized, Placebo-Controlled Multiple Ascending Dose Study

Study Objectives:

- Evaluate the safety and tolerability of AMX0114 administered intrathecally for a total of up to 4 doses per dose level
- Evaluate the pharmacokinetics of AMX0114 in CSF and plasma
- Assess the effects of AMX0114 on plasma and CSF biomarkers and functional measures of ALS disease progression

Key Trial Entry Criteria

- ✓ ≥ 18 years of age
- ✓ Diagnosis of clinically definite or clinically probable ALS, based on El Escorial criteria
- ✓ <24 month since onset of first ALS symptom
- ✓ Slow vital capacity (SVC) ≥ 65%
- ✓ Approved treatments for ALS are allowed if participant is on a stable dose for at least 30 days prior to baseline visit

~ 48 adult participants with ALS

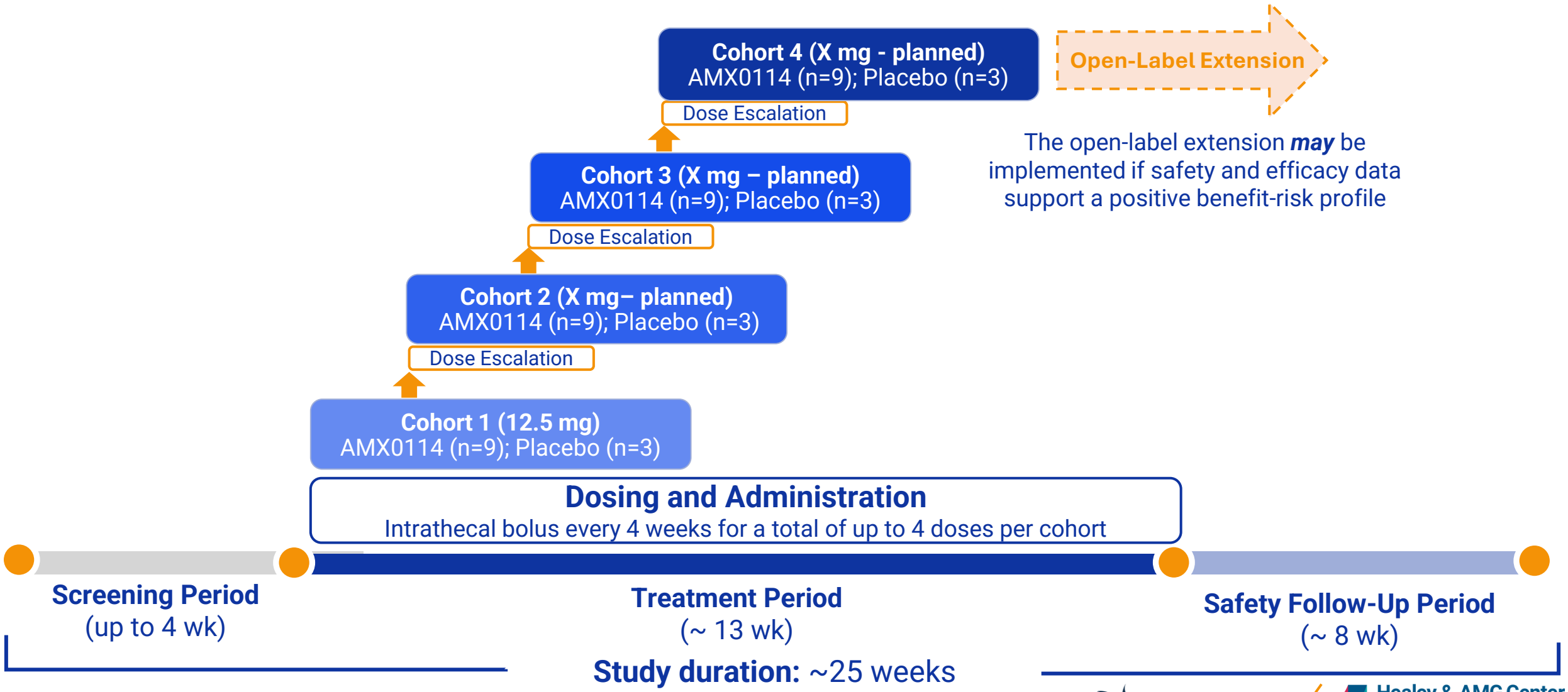
Investigators:
Marvin Chum, MD
Angela Genge, MD
Wymer James, MD
Collin Luk, MD, PhD
Shakti Nayar, MD
Bjorn Oskarsson, MD
Sabrina Paganoni, MD, PhD
John Ravits, MD
Shroff Sheetal, MD
Christen Shoesmith, MD
Eric Sorenson, MD
Vahid Tohidi, MD, PhD
Randall Trudell, MD

Map created with MapChart.

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

LUMINA Multiple Ascending Dose Study Design



For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

LUMINA Study 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

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

Tertiary Endpoints

Pharmacodynamics/Biomarkers

- Change from baseline of plasma and CSF pharmacodynamic measures of ALS and markers of target engagement (e.g., calpain-2 levels, NfL, SBDP-145)

ALS Progression Measures

- Change from baseline of ALS Functional Rating Scale – Revised (ALSFRS-R) and slow vital capacity (SVC)

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

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

Key Takeaways

Calpain-2 is a critical effector of axonal degeneration, a key early contributor to the pathogenesis of amyotrophic lateral sclerosis

AMX0114 is an ASO that achieves robust knockdown of calpain-2 mRNA and protein across multiple disease-relevant cell types and models of axonal degeneration and neuronal death

In preclinical models, **AMX0114 has shown dose-dependent improvements in neuronal survival** and NfL

The LUMINA phase 1 trial evaluating the safety and tolerability of AMX0114 in adults with ALS is ongoing; additional data updates expected later this year

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX / Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

LUMINA

Scan to Learn More about the LUMINA Trial

We extend our deepest gratitude to trial participants as well as the ALS clinicians, NEALS SAB, people living with ALS, and caregivers who provided feedback and advice on the study design.

QUESTIONS?

Join Tonight's Lightning Talks and Visit Poster #11 to Explore:

- Biomarkers of calpain-2 activity in ALS
- The impact of AMX0114 in preclinical models

For Scientific meeting use only. Do not duplicate, distribute, or disseminate. Copyright © 2025 Amylyx Pharmaceuticals, Inc.

AMYLYX

Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital