



# AMX0114 ALS Study Update

**Lauren Kett, MD, PhD**

Vice President, Clinical Development  
*Amylyx Pharmaceuticals*

**Sabrina Paganoni, MD, PhD**

Co-Director, Neurological Clinical Research Institute  
*Sean M. Healey & AMG Center for ALS at MGH*

# Investigational Status and Disclosures

- 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 Pharmaceuticals, 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.

# Multiple Lines of Evidence Implicate Calpain-2 in ALS-Associated Axonal Degeneration

## Evidence Linking Calpain-2 to ALS



### Calpain-2 Dysregulation in ALS

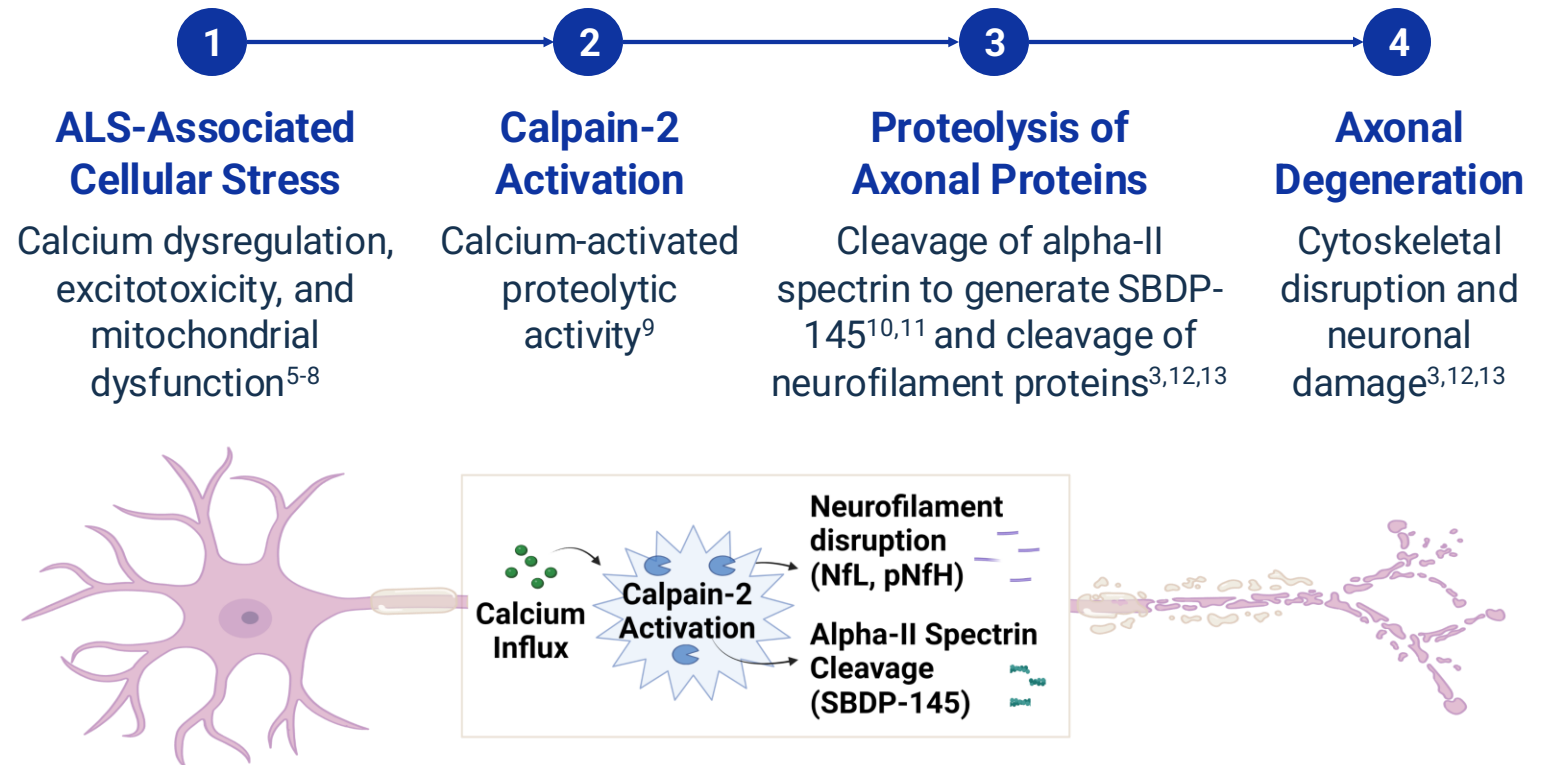
Elevated CAPN2 expression, increased calpain-specific cleavage products, and rare CAPN2 variants are associated with increased risk of ALS<sup>1-4</sup>



### Convergence with ALS Pathways

Calpain-2 contributes to excitotoxicity, mitochondrial dysfunction, neuroinflammation, and impaired nucleocytoplasmic transport – key intersecting mechanisms in ALS pathogenesis<sup>5-8</sup>

## PROPOSED MECHANISTIC FRAMEWORK

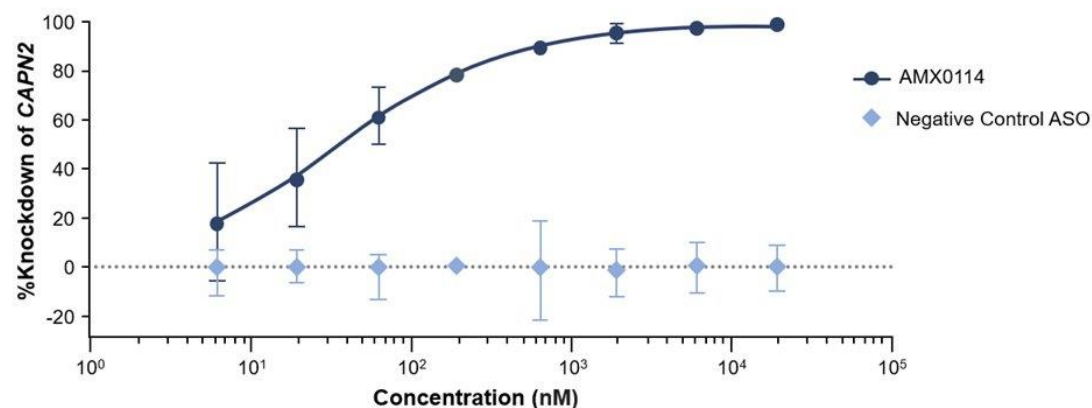


1. Ueyama et al. *J Neurol Sci*. 1998. 2. Yamashita et al., *Nat Commun*. 2012. 3. Rao et al., *J Neurochem*. 2016. 4. Hop et al., *Nature Genetics*. 2026. 5. Tadic et al., *Front. Cell. Neurosci*. 2014. 6. Yamashita et al., *Sci Rep*. 2017. 7. Knaryan & Sarukhanyan, *Neurosci Behav Physiol*. 2024. 8. Smith & Schnellmann, *Cardiovascular Research*. 2012. 9. Ono et al., *Nat Rev Drug Discov*. 2016. 10. Zhang Z, et al. *Apoptosis*. 2009; 14:1289-1298. 11. McGinn M, et al., *J Neuropathol Exp Neurol*. 2009. 12. Ma M., *Neurobiol Dis*. 2013. 13. Ma M, et al., *Neurobiol Dis*. 2013. Figure created in BioRender. Fontaine, R. (2026) <https://BioRender.com/yozlrea>

# AMX0114 Was Designed to Selectively Reduce Calpain-2 and Has Demonstrated Neuroprotective Effects in Preclinical Models

## TARGET ENGAGEMENT

**AMX0114 achieved potent, dose-dependent, and durable knockdown of *CAPN2* mRNA and calpain-2 protein<sup>1</sup>**



### Selective Targeting

AMX0114 is designed to target *CAPN2* while preserving the function of other calpains and calpastatin

## DOWNSTREAM PRECLINICAL EFFECTS



### Reduced Extracellular NfL

in trigger-induced neuronal injury and a model of TDP-43 ALS<sup>1,2</sup>



### Improved Neuronal Survival

in a model of TDP-43 ALS<sup>2</sup>



### Demonstrated Neuroprotective Effects

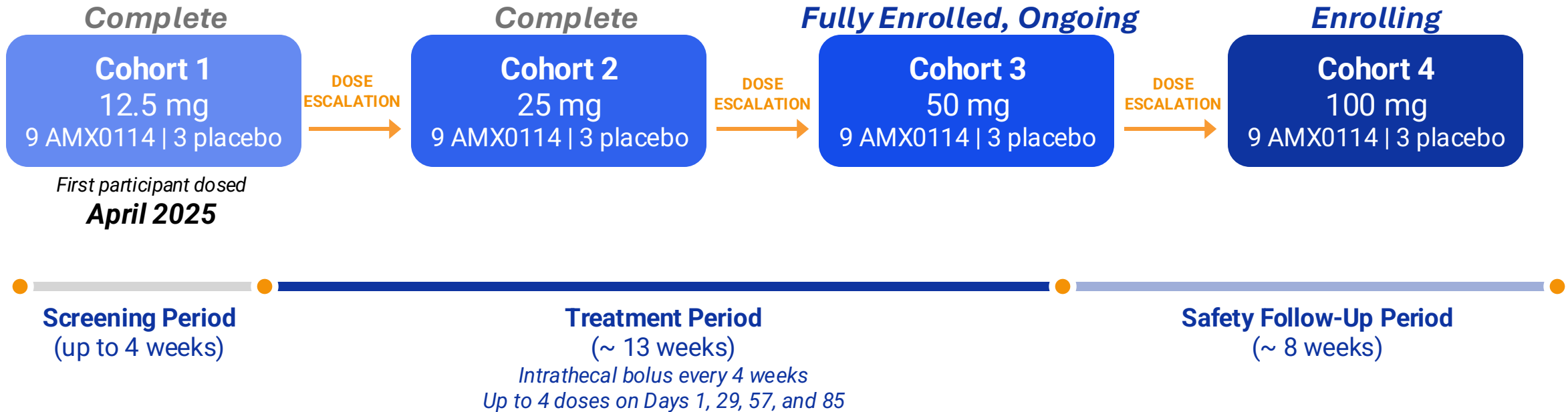
in a model of oxidant-induced cell death<sup>2</sup>

*CAPN2*, calpain-2; NfL, neurofilament light chain

1. Cohen J, et al. Presented at the 22<sup>nd</sup> Annual NEALS Meeting; Clearwater Beach, Florida; October 4-6, 2023. 2. Mizerak E, et al. Presented at the TIDES USA Conference; Boston, MA; May 14-17, 2024.

# LUMINA Phase 1 Multiple Ascending Dose Study Design

Randomized, placebo-controlled, multicenter study of AMX0114 in adults with ALS



## Key Trial Entry Criteria

- ≥18 years old
- Clinically definite/probable ALS
- <24 months since onset of first ALS symptom
- SVC ≥65%
- On stable ALS therapy ≥30 days

## Study Endpoints



### Primary

Safety and tolerability



### Secondary

Pharmacokinetics

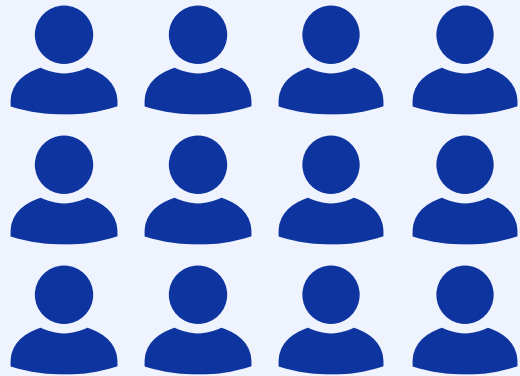


### Exploratory

**Biomarkers:** Target engagement and disease  
**Clinical Measures:** ALSFRS-R and SVC

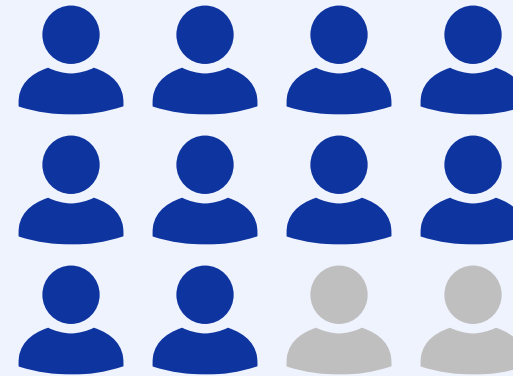
# Participant Disposition

## Cohort 1



**12 of 12**  
completed  
the treatment period

## Cohort 2



**10 of 12**  
completed  
the treatment period

### Withdrawals

- 2 participants withdrew; neither withdrew due to an adverse event or death

### Dose Exposure

- 10 participants received all 4 doses
- 1 participant received 3 doses
- 1 participant received 2 doses

# Cohort 1 and 2: Baseline Characteristics

|                                              |                     | Cohort 1 (n=12) | Cohort 2 (n=12) |
|----------------------------------------------|---------------------|-----------------|-----------------|
| <b>DEMOGRAPHICS</b>                          |                     |                 |                 |
| <b>Age (years)</b>                           |                     | 62.5 ± 9.99     | 58.8 ± 7.86     |
| <b>Sex – n (%)</b>                           | Male                | 9 (75.0%)       | 11 (92%)        |
|                                              | Female              | 3 (25.0%)       | 1 (8%)          |
| <b>BMI (kg/m<sup>2</sup>)</b>                |                     | 28.2 ± 4.03     | 27.3 ± 5.81     |
| <b>ALS DISEASE CHARACTERISTICS</b>           |                     |                 |                 |
| <b>Site of Onset – n (%)</b>                 | Bulbar              | 1 (8.3%)        | -               |
|                                              | Cervical            | 7 (58.3%)       | 8 (66.7%)       |
|                                              | Lumbrosacral        | 4 (33.3%)       | 3 (25%)         |
|                                              | Generalized         | -               | 1 (8.3%)        |
| <b>Time Since Symptom Onset (months)</b>     |                     | 14.0 ± 4.20     | 15.4 ± 4.42     |
| <b>El Escorial Criteria</b>                  | Clinically Definite | 3 (25.0%)       | 5 (41.7%)       |
|                                              | Clinically Probable | 9 (75.0%)       | 7 (58.3%)       |
| <b>ALSFRS-R Total Score</b>                  |                     | 39.0 ± 4.95     | 38.9 ± 6.22     |
| <b>SVC (% Predicted)</b>                     |                     | 90.4 ± 11.39    | 93.6 ± 21.92    |
| <b>Stable Use of ALS Medications – n (%)</b> | Riluzole            | 9 (75.0%)       | 11 (91.7%)      |
|                                              | Edaravone           | 5 (41.7%)       | 6 (50.0%)       |
| <b>BIOMARKER AND GENETIC CHARACTERISTICS</b> |                     |                 |                 |
| <b>ALS Gene Variant Identified* - n (%)</b>  |                     | 3 (25.0%)       | 2 (16.7%)       |
| <b>Baseline CSF NfL (pg/mL) – mean (SE)</b>  |                     | 12,385 (2700)   | 10,124 (1527)   |

Plus/minus values are means ± SD

\*ALS gene variants identified include: ATXN2, C9ORF72, and variant of unknown significance in SETX and UNC13A

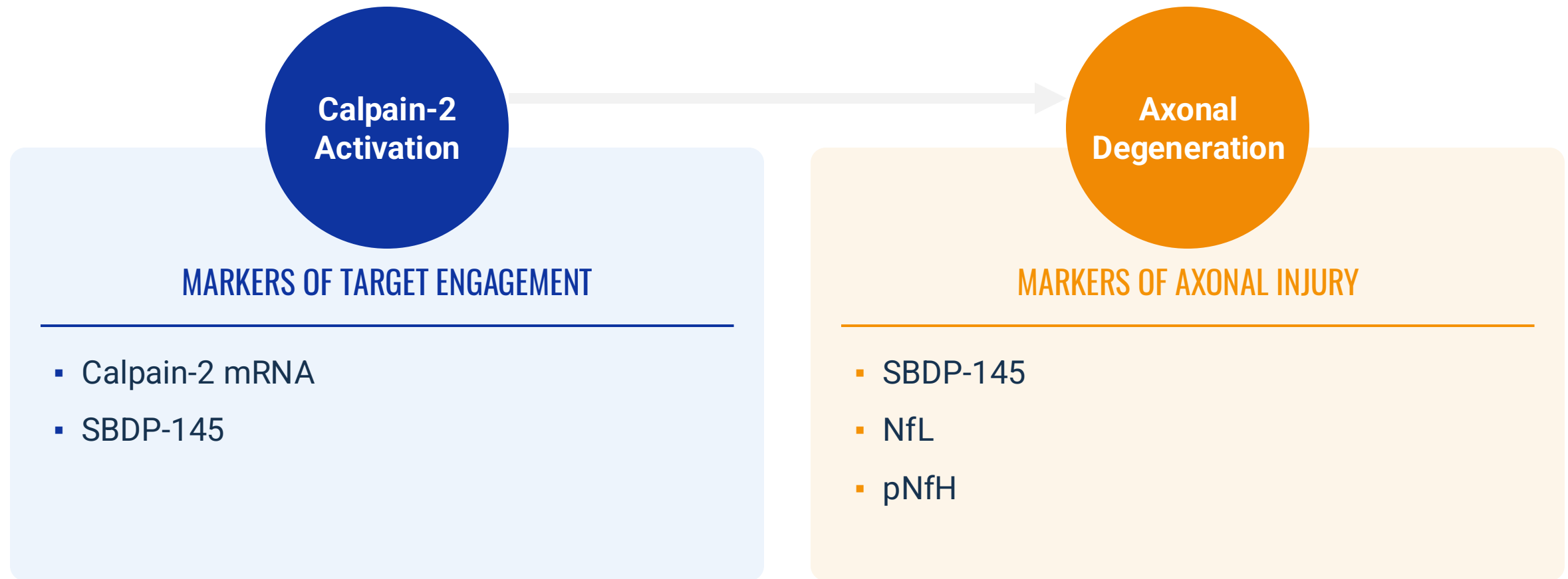
# No drug-related serious TEAEs, dose-limiting toxicities, dose modifications, or serious neurological AEs across Cohort 1 or 2

| Cohort 1 & 2 Safety                                                                           | AMX0114<br>(12.5 mg) (n=9)<br>n (%) | AMX0114<br>(25 mg) (n=9)<br>n (%) | Placebo<br>(n=6)<br>n (%) |
|-----------------------------------------------------------------------------------------------|-------------------------------------|-----------------------------------|---------------------------|
| Any Treatment-Emergent Adverse Event (TEAE)                                                   | 9 (100%)                            | 9 (100%)                          | 6 (100%)                  |
| Drug-Related TEAE                                                                             | 4 (44%)                             | 6 (67%)                           | 2 (33%)                   |
| Procedure-Related TEAE                                                                        | 5 (56%)                             | 8 (89%)                           | 5 (83%)                   |
| Drug-Related Serious TEAE                                                                     | 0                                   | 0                                 | 0                         |
| Dose-Limiting Toxicity                                                                        | 0                                   | 0                                 | 0                         |
| TEAEs Leading To Dose Change<br><i>Reduction, interruption, discontinuation, modification</i> | 0                                   | 0                                 | 0                         |
| TEAEs of Interest                                                                             |                                     |                                   |                           |
| Nervous System Disorders ( <i>mild to moderate</i> )                                          | 5 (56%)                             | 4 (44%)                           | 2 (33%)                   |
| Nervous System Disorders ( <i>severe to fatal</i> )                                           | 0                                   | 0                                 | 0                         |
| General/Admin Site Conditions ( <i>mild to moderate</i> )                                     | 5 (56%)                             | 5 (56%)                           | 2 (33%)                   |

- TEAEs of interest included headache and lower-extremity nerve pain; reported events were **acute and mild to moderate in intensity**
- **Procedure-related events** (e.g., post-lumbar puncture syndrome) **occurred in both** AMX0114 and placebo groups **and were more frequent than drug-related TEAEs**
- **No drug-related serious TEAEs were reported**
- **No serious neurologic AEs were reported**
- **No laboratory abnormalities of interest or abnormalities meeting stopping criteria** in Cohort 1 or 2

# Calpain-2 Substrates Enable a Unique Exploratory Biomarker Strategy

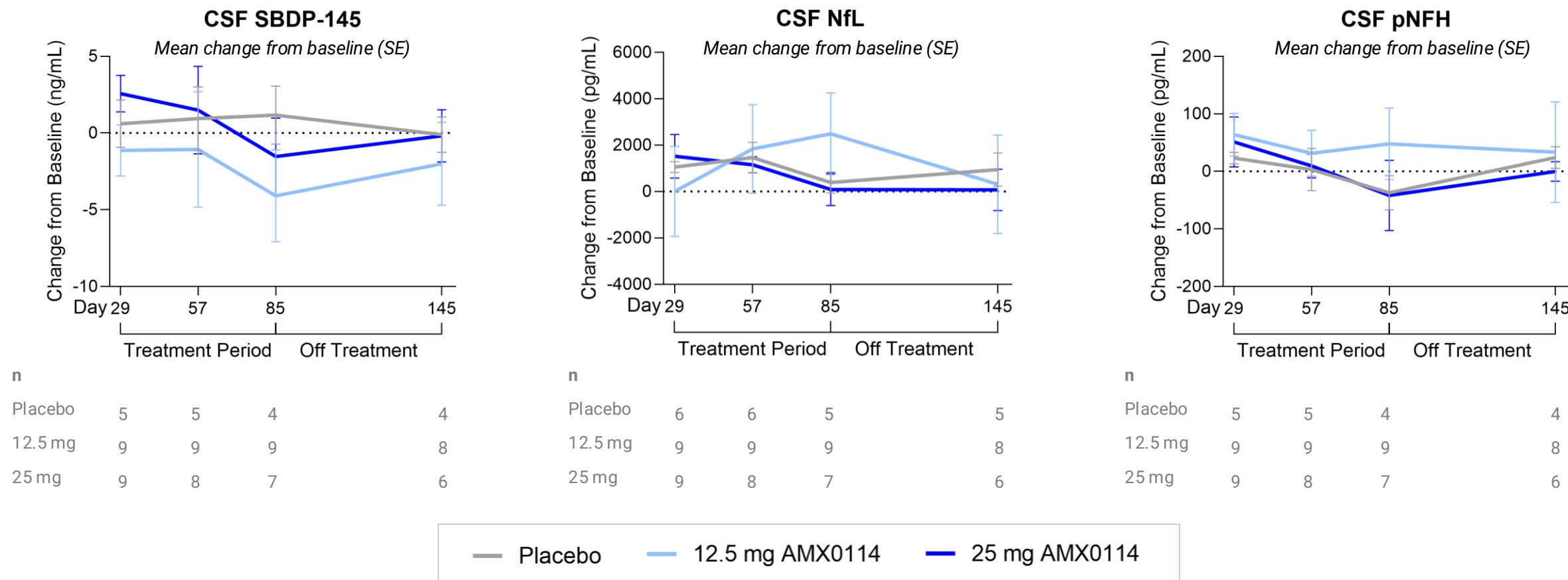
Safety and tolerability are the primary focus of LUMINA; exploratory biomarkers assess AMX0114 target engagement, axonal injury, and relationships with disease progression



Calpain-2 mRNA method qualified  
SBDP-145, spectrin breakdown product 145; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain

# No consistent biomarker changes at the lowest AMX0114 doses evaluated

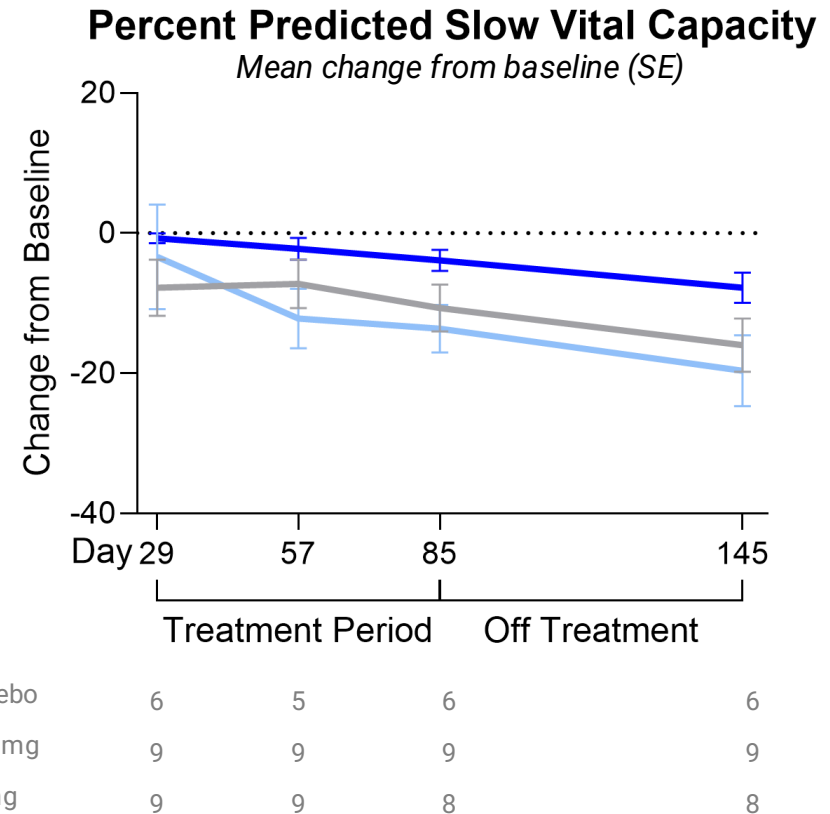
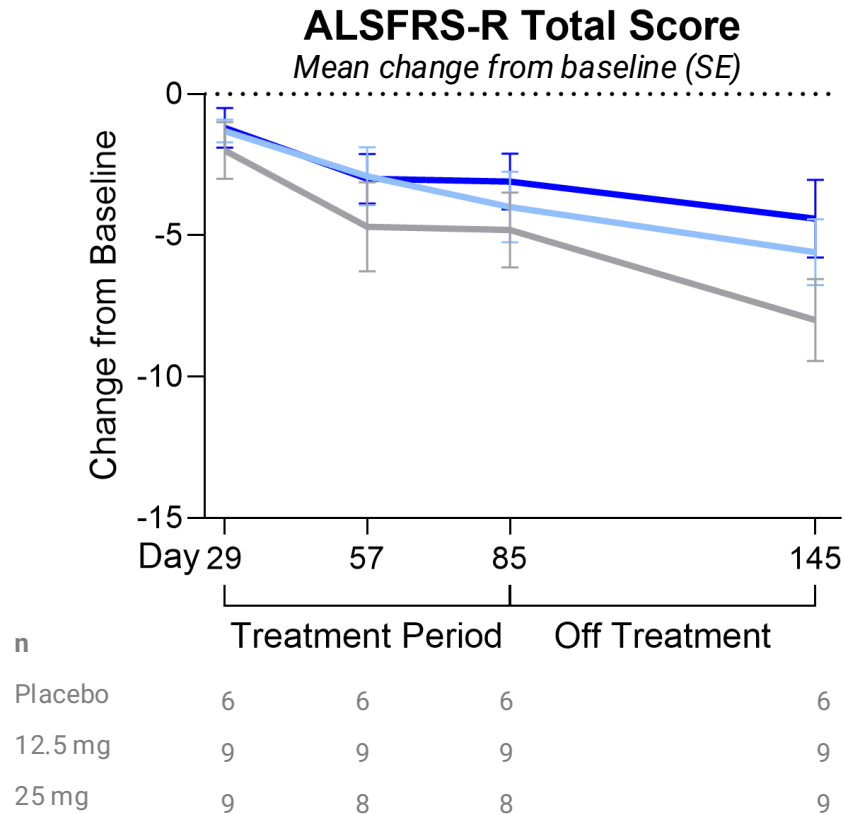
Exploratory biomarker findings may reflect limited exposure and/or treatment duration



n represents participants with evaluable measurements at each timepoint. CSF SBDP-145 and pNFH were measured using ELISA qualified fit-for-purpose following ICH M10, matrix-matched standard curves with appropriate controls and met predefined criteria for accuracy, precision, linearity, spike recovery. CSF NfL was measured using ultra-sensitive Simoa N2PB Advantage Plus (Quanterix) validated fit-for-purpose for precision, spike recovery, dilution linearity, and stability. Analytical range: CSF SBDP-145: 0.625-40 ng/mL; CSF pNFH: 1.2-5,000 pg/mL; CSF NfL: 161-180,000 pg/mL.

# No difference in clinical measures at the lowest AMX0114 doses evaluated

Interpretation is limited by the exploratory design and small sample size



— Placebo    — 12.5 mg AMX0114    — 25 mg AMX0114

n represents participants with evaluable measurements at each timepoint.

# Trial Learnings: Enabling Efficient, Participant-Centered Study Execution

1

## Close Site Partnership Enabled Efficient Recruitment

Frequent, transparent communication helped sites understand enrollment timing and participant waitlist status. Regular touchpoints included closed NEALS sessions, monthly site calls, targeted communications, and direct coordination with study teams.

2

## Participant and Caregiver Support Helped Make Participation More Feasible

Educational materials and dedicated caregiver resources were paired with practical accommodations, including overnight caregiver stays during 24-hour visits, flexible travel arrangements, and transfers between study sites when needed to minimize travel burden.

3

## Multidisciplinary Expertise Guided Dose Escalation

The Dose Escalation Committee integrated expertise across ALS, neurodegeneration, and ASO development. Experience from ASO trials within and beyond ALS helped contextualize emerging findings and inform dose-escalation decisions.

*We thank the LUMINA investigators, study coordinators, participants, and caregivers whose engagement continues to make this progress possible*

# Key Takeaways



**AMX0114 targets calpain-2**, a key driver of axonal degeneration, with preclinical studies supporting target engagement and neuroprotective effects



**LUMINA continues to progress**, with Cohorts 1 and 2 complete, Cohort 3 fully enrolled and ongoing, and Cohort 4 actively enrolling



**AMX0114 has been generally well tolerated across evaluated dose cohorts**, supporting ongoing clinical evaluation



**Exploratory CSF biomarker findings remain preliminary**; ongoing evaluation of higher-dose cohorts may help clarify potential dose-dependent biological effects

# THANK YOU

We are grateful to the trial participants, people living with ALS, caregivers, clinicians, site teams, the NEALS Scientific Advisory Board, and advisors whose partnership has made the LUMINA study possible



Map created with MapChart.

# QUESTIONS?



Learn more about the **LUMINA** trial

| Participating Investigators and Study Sites                                                              |                                                                                                    |                                                                                                           |
|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Marvin Chum, MD</b><br>McMaster University                                                            | <b>Shakti Nayar, MD</b><br>Georgetown University Hospital<br>Pasquerilla Healthcare Center         | <b>Christen Shoesmith, MD</b><br>London Health Sciences Centre                                            |
| <b>Angela Genge, MD</b><br>McGill University Health Centre – Centre<br>for Innovative Medicine           | <b>Bjorn Oskarsson, MD</b><br>Mayo Clinic, Florida                                                 | <b>Eric Sorenson, MD</b><br>Mayo Clinic, Rochester                                                        |
| <b>Terry Heiman-Patterson, MD</b><br>Temple University of the Commonwealth<br>System of Higher Education | <b>Sabrina Paganoni, MD, PhD</b><br>Massachusetts General Hospital, Healey<br>& AMG Center for ALS | <b>Vahid Tohidi, MD, PhD</b><br>Orlando Regional Medical Center,<br>Orlando Health Neuroscience Institute |
| <b>Shafeeq Ladha, MD</b><br>Barrow Neurological Institute                                                | <b>John Ravits, MD</b><br>University of California, San Diego                                      | <b>Randall Trudell, MD</b><br>Alliance for Multispecialty Research, LLC                                   |
| <b>Collin Luk, MD, PhD</b><br>University of Calgary                                                      | <b>Sheetal Shroff, MD</b><br>Houston Methodist Neurological Institute                              | <b>James Wymer, MD</b><br>University of Florida                                                           |