Initial Safety Findings from the Phase 1 LUMINA Trial of AMX0114 in Amyotrophic Lateral Sclerosis

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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

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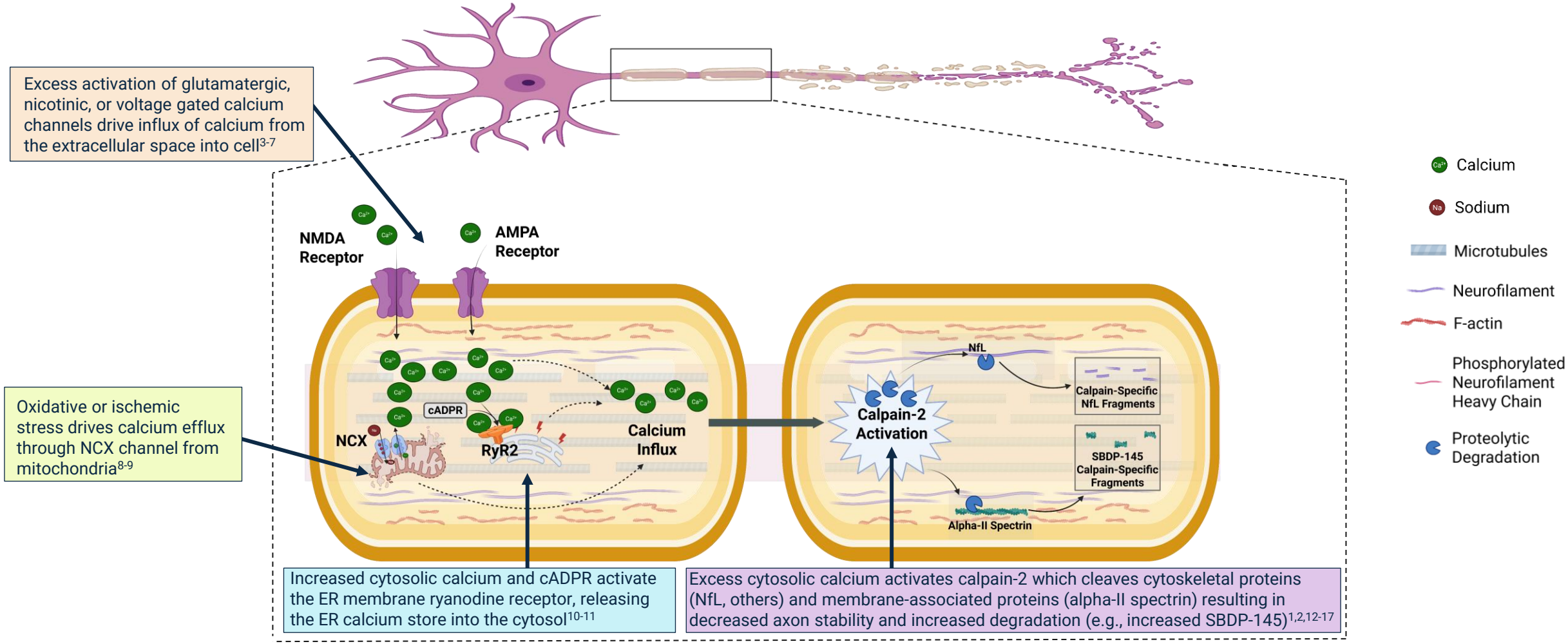
Axonal Degeneration is a Key Early Contributor to ALS Pathogenesis[1,2]



AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cADPR, cyclic adenosine diphosphate ribose; ER, endoplasmic reticulum; NCX, sodium-calcium exchanger; NfL, neurofilament light chain; NMDA, N-methyl-D-aspartate; RyR2, ryanodine receptor 2; SBDP-145, alpha-II spectrin breakdown product 145 kDa; Created in BioRender. Fontaine, R. (2026)

1. Moloney et al., *Front Neurosci* 2014. **2.** Ma, *Neurobiol Dis* 2013. **3.** Keller et al., *EMBO J.* 1992. **4.** Lu et al., *J. Neurosci* 1996. **5.** Shen & Yakel., *Acta Pharmacol Sin* 2009. **6.** Vernino et al., *Neuron* 1992. **7.** Simms & Zamponi., *Neuron* 2014. **8.** Scognamiglio et al., *Int J Mol Sci* 2025. **9.** Brini et al., *Cell Mol Life Sci.* 2014. **10.** Fill and Copello., *Physiol. Rev.* 2002. **11.** Takasawa *Int. J. Mol. Sci.* 2022. **12.** Wang et al., *Cells*. 2020. **13**. Asakawa et al., *Cell Mol Life Sci.* 2021. **14.** Ueyama et al., *J Neurol Sci.* 1998. **15**. Yamashita et al., *Nat Commun*. 2012. **16**. Rao et al. *J Neurochem*. 2016. **17.** Czogalla & Sikorski. *Cell Mol Life Sci*. 2005.

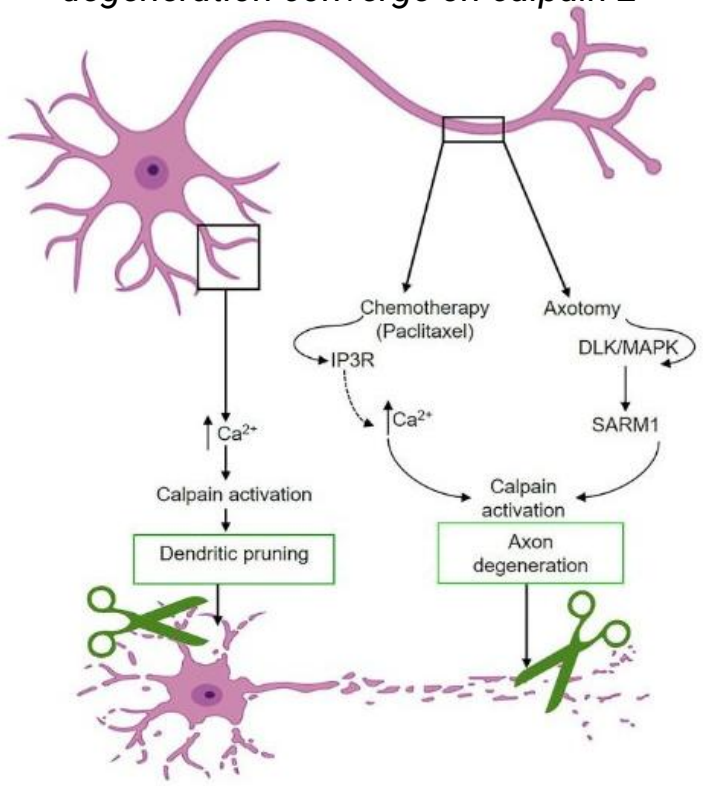
Calpain-2, a Ca^{2+}-Activated Cysteine Protease, Drives Axonal Degeneration and Contributes to the Pathogenesis of ALS

Importance of Calpain-2 in ALS

- **Effector of Axonal Degeneration**[1-6]
  Calpain-2 is a calcium-dependent protease that drives early axonal degeneration by cleaving cytoskeletal proteins such as αII-spectrin and NfL
- **Mechanistic Link to ALS Pathways**[8-11]
  Calpain-2 contributes to excitotoxicity, mitochondrial dysfunction, neuroinflammation, and impaired nucleocytoplasmic transport — key intersecting mechanisms in ALS pathogenesis
- **Unique Target In ALS**[4-7]
  - *CAPN2* mRNA is elevated in muscle and calpain-specific cleavage products are increased in the spinal cord and brain of people with ALS
  - Emerging exome analyses indicate that rare *CAPN2* variants may contribute to ALS risk
  - In the SOD1G93A mouse model, calpain-2 inhibition increased overall survival and delayed disease onset

Mechanisms of Axonal Degeneration[12]

Multiple injury paradigms and hypotheses of axonal degeneration converge on calpain-2



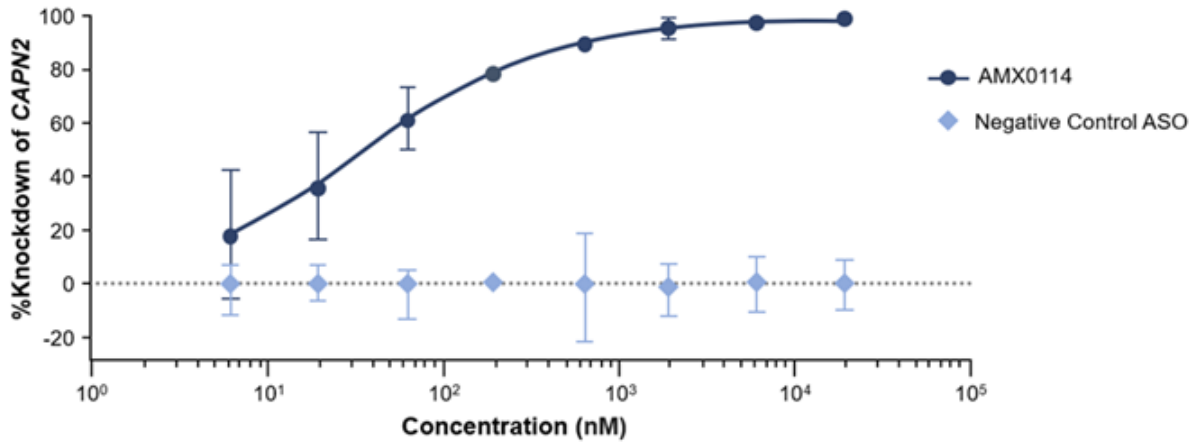
NfL, Neurofilament light chain

1. Moloney et al., *Front Neurosci*. 2014. **2**. Ma, *Neurobiol Dis*. 2013. **3**. Asakawa et al., *Cell Mol Life Sci*. 2021. **4**. Ueyama et al. *J Neurol Sci.* 1998. **5**. Yamashita et al., *Nat Commun*. 2012. **6**. Rao et al., *J Neurochem.* 2016. **7**. Hop et al., *Amyotroph. Lateral Scler. Frontotemporal Degener*. 2025. **8**. Tadic et al., *Front. Cell. Neurosci*. 2014. **9**. Yamashita et al., *Sci Rep.* 2017. **10**. Knaryan & Sarukhanyan, *Neurosci Behav Physiol.* 2024. **11**. Smith & Schnellmann, *Cardiovascular Research.* 2012. **12**. Metwally et al., *Front. Vet Sci.* 2023.

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

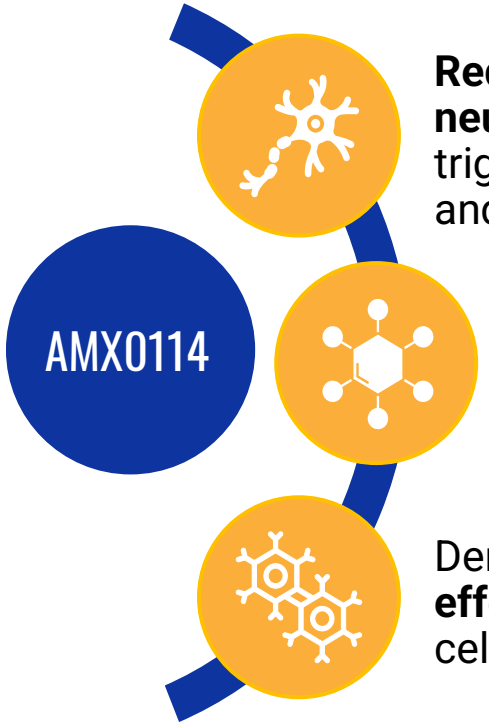
Target Engagement Observed in in vitro ALS Models

AMX0114 achieves potent, dose-dependent, and durable knockdown of *CAPN2* mRNA and calpain-2 protein[1].



The selective ASO modality allows for inhibition of calpain-2 without disrupting the function of other calpains or calpastatin

Neuroprotective Effects Observed in in vitro ALS Models



Reduced extracellular neurofilament light chain (NfL) in trigger-induced neuronal injury and model of TDP-43 ALS[1,2]

Improved neuron survival in model of TDP-43 ALS[2]

Demonstrated **neuroprotective effects** in model of oxidant-induced cell death[2]

1. Cohen J, et al. Presented at the 22nd 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 Is a Phase 1, Multicenter, Randomized, Placebo-Controlled Multiple Ascending Dose Study

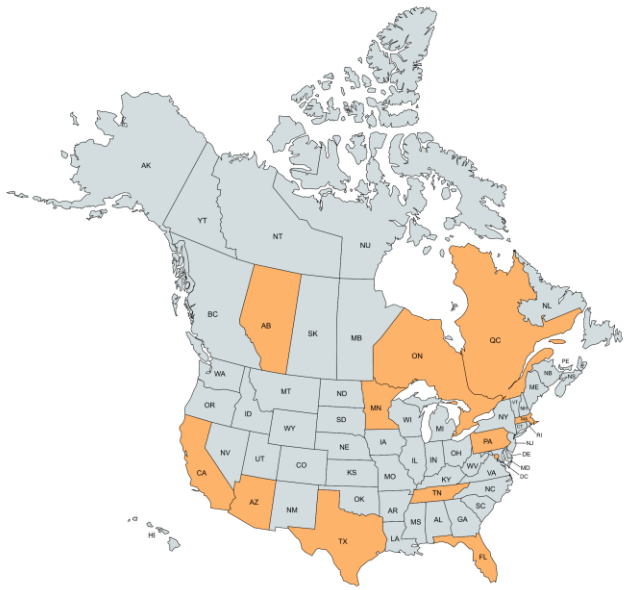
Study Objectives:

- 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%[1]
- ✓ Approved treatments for ALS are allowed if participant is on a stable dose for at least 30 days prior to baseline visit

LUMINA will be conducted at ~15 sites in Canada and the United States, enrolling ~48 adult participants with ALS



Investigators:

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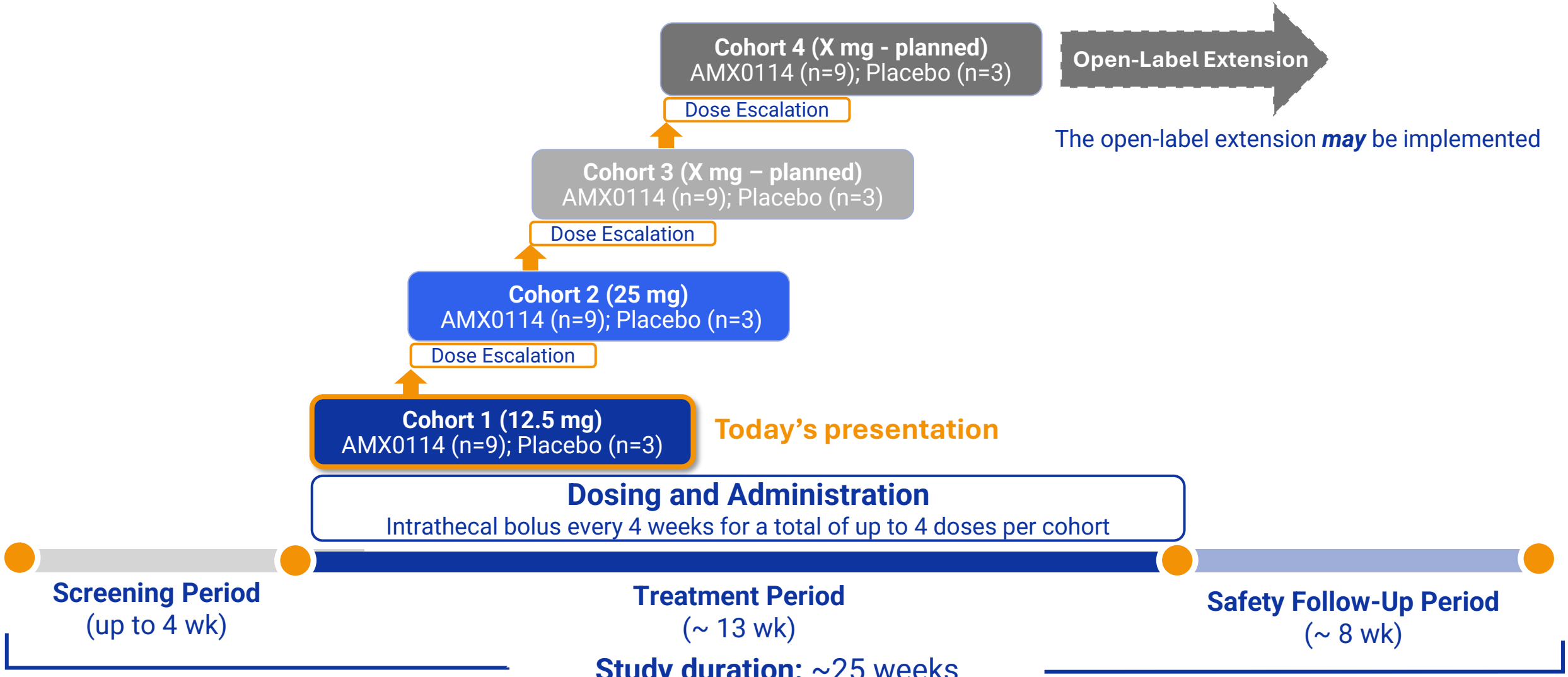
- Bjorn Oskarsson, MD
- Sabrina Paganoni, MD, PhD
- John Ravits, MD
- Christen Shoesmith, MD
- Sheetal Shroff, MD
- Eric Sorenson, MD
- Vahid Tohidi, MD, PhD
- Randall Trudell, MD
- James Wymer, MD

[1]Protocol amendment reduced SVC threshold from 75% to 65% | Map created with MapChart

LUMINA Multiple Ascending Dose Study Design



The first 2 participants were dosed as a sentinel group. Following sentinel dosing, a ~48-hour safety review period occurred before dosing of the next participant was approved.

LUMINA Cohort 1: Baseline Characteristics

All 12 randomized Cohort 1 participants completed the treatment period; no discontinuations occurred.

Baseline Parameter		Cohort 1 Participants (n=12)
Age (years), **mean** (SD)		**62.5** (9.99)
Sex – n (%)	Male	**9** (75.0%)
	Female	**3** (25.0%)
BMI (kg/m^2) – **mean** (SD)		**28.2** (4.03)
Site of Onset – n (%)	Cervical	**7** (58.3%)
	Lumbosacral	**4** (33.3%)
	Bulbar	**1** (8.3%)
Time Since Symptom Onset (months) – **mean** (SD)		**14.0** (4.20)
ALSFRS-R Total Score – **mean** (SD)		**39.0** (4.95)
SVC (% Predicted) – **mean** (SD)		**90.4%** (11.39%)
ALS Gene Variant Identified – **n** (%)		**3** (25.0%)
Stable Use of ALS Medications – **n** (%)	Riluzole	**9** (75.0%)
	Edaravone	**5** (41.7%)

LUMINA Cohort 1: Safety Profile

All 12 Cohort 1 participants completed all 4 doses with no drug-related serious TEAEs, no dose-limiting toxicities, no dose modifications, and no serious neurological AEs

	AMX0114 (12.5 mg) (n=9) n (%)	Placebo (n=3) n (%)
Any Treatment-Emergent Adverse Event (TEAE)	**8** (89%)	**3** (100%)
Drug-Related TEAE	**4** (44%)	**2** (67%)
Procedure-Related TEAE	**5** (56%)	**2** (67%)
Drug-Related Serious TEAE	**0**	**0**
Dose-Limiting Toxicity	**0**	**0**
TEAEs Leading To Dose Change *Reduction, interruption, discontinuation, modification*	**0**	**0**
TEAEs of Interest Nervous System Disorders (*mild to moderate)* Nervous System Disorders (*severe to fatal*) General/Admin Site Conditions (*mild to moderate)*	 **6** (67%) **0** **5** (56%)	 **2** (67%) **0** **1** (33%)
Laboratory Abnormalities of Interest *ALT, AST, creatinine, platelets, INR, aPTT*	**0**	**0**

- **Most TEAEs mild**
- Observed TEAEs of interest included **headache and fatigue**
- **Procedure-related events** (e.g., post-LP syndrome) **occurred in both** AMX0114 and placebo groups **and were more frequent than drug-related events**
- **No drug-related serious adverse events**
- **No serious neurologic adverse events reported**

ULN, Upper Limit of Normal ; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; INR, International Normalized Ratio*; aPTT, Activated Partial Thromboplastin Time; LP, Lumbar Puncture*
Any categories with 1 event not disclosed to protect participant and investigator blinding. Expanded safety information to be disclosed upon addition of further cohorts.
Related events include TEAEs assessed by the investigator as possibly, probably, or definitely related to the study drug/procedure.

Key Takeaways

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

AMX0114 is an ASO that achieves robust knockdown of calpain-2 mRNA and protein, improves neuronal survival, and reduces extracellular NfL across multiple disease-relevant cell models

AMX0114 (12.5 mg) was generally well-tolerated in the Phase 1 LUMINA trial, with no drug-related SAEs and no serious neurological AEs in Cohort 1

These data have provided support to the dose escalation committee to recommend continuing to Cohort 2, which is enrolling.

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.

LUMINA

Scan to Learn More about the LUMINA Trial