LUMINA Advancing AMX0114 for ALS: Updates From The LUMINA Phase 1 Study

AMYLYX

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Sabrina Paganoni, MD, PhD[1,2]; Lauren Kett, MD, PhD[3]; Robert Bowser, PhD[4]; Elaina Breznau, PhD[3]; Lauren Kingston[3]; John Pesko, PhD[3]; Rebecca Fontaine, PhD[3]; Jamie Timmons, MD[3], Angela Genge, MD[5]

[1]Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [2]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, Massachusetts, USA; [3]Amylyx Pharmaceuticals, Inc., Cambridge, Massachusetts, USA [4]Barrow Neurological Institute, Phoenix, Arizona, USA; [5]Department of Neurology, Montreal Neurological Institute, Montreal, Quebec, CA

Background

Role of Calpain-2 in Axonal Degeneration

- Calpain-2 is a calcium-activated cysteine protease upregulated in ALS and a critical effector of **axonal degeneration**[1-7]
- Pathologic activation leads to proteolysis of neuronal skeletal proteins, resulting in:
  - Generation of spectrin breakdown product 145 (**SBDP-145**) – a direct marker of calpain activity[8-9]
  - Release of axonal injury biomarkers including neurofilament light (**NfL**) and phosphorylated neurofilament heavy (**pNfH**)[3,5-6]
  - Progressive cytoskeletal disruption and neuronal damage[3,5-6]

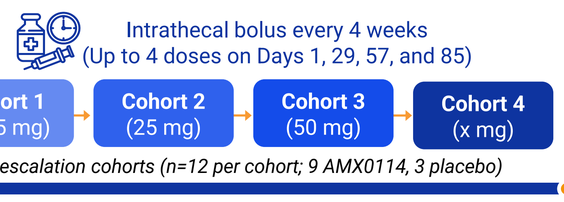
AMX0114: Targeted Intervention

AMX0114 is an investigational ASO designed to reduce *CAPN2* expression, addressing a key upstream mechanism of neurodegeneration. In preclinical models, AMX0114 showed:

- Robust, dose-dependent reduction of *CAPN2* mRNA and calpain-2 protein[10]
- Reduced extracellular NfL[11]
- Improved neuronal survival and demonstrated neuroprotective effects[11]

LUMINA Trial Overview

Phase 1 randomized, placebo-controlled, multicenter, multiple ascending dose study of AMX0114 in ALS



Key Trial Entry Criteria:

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

An open-label extension *may* be implemented if safety and efficacy data support a positive benefit-risk profile

Study Status:

Cohort 1 Complete | Cohort 2 Fully Enrolled | Cohort 3 Enrolling

LUMINA Endpoints

Primary	• Incidence of adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities (DLTs) • Abnormalities in clinical labs, vital signs, physical and neurological exams, ECGs
Secondary	• PK concentrations of AMX0114 (plasma & CSF)
Tertiary	• Markers of target engagement (plasma & CSF): NfL, calpain-2, SBDP-145, pNFH • ALSFRS-R & SVC change from baseline

Biomarker Assay Methods

CSF biomarkers (SBDP-145, pNfH)

- ELISA qualified fit-for-purpose following ICH M10
- Matrix-matched standard curves with appropriate controls (spiked QCs, endogenous ALS CSF, negative controls)
- Assay performance met predefined criteria (accuracy, precision, linearity, spike recovery)
- Analytical range:
  - SBDP-145: 0.625–40 ng/mL
  - pNfH: 1.2–5,000 pg/mL

Neurofilament light chain (NfL; plasma and CSF)

- Measured using ultra-sensitive Simoa (Quanterix HD-1 platform)
- Validated fit-for-purpose for precision, spike recovery, and dilutional linearity, stability
- Analytical range:
  - Plasma: 0.45–1,412 pg/mL
  - CSF: 11–35,300 pg/mL

Assay considerations

- All assays met predefined validation criteria
- Short-term stability was variable (24-hour decline observed under some conditions)
- Updated Simoa assay at different vendor selected for future cohorts; Cohort 1 data to be reanalyzed across assays

LUMINA Cohort 1 Baseline Characteristics

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%)

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

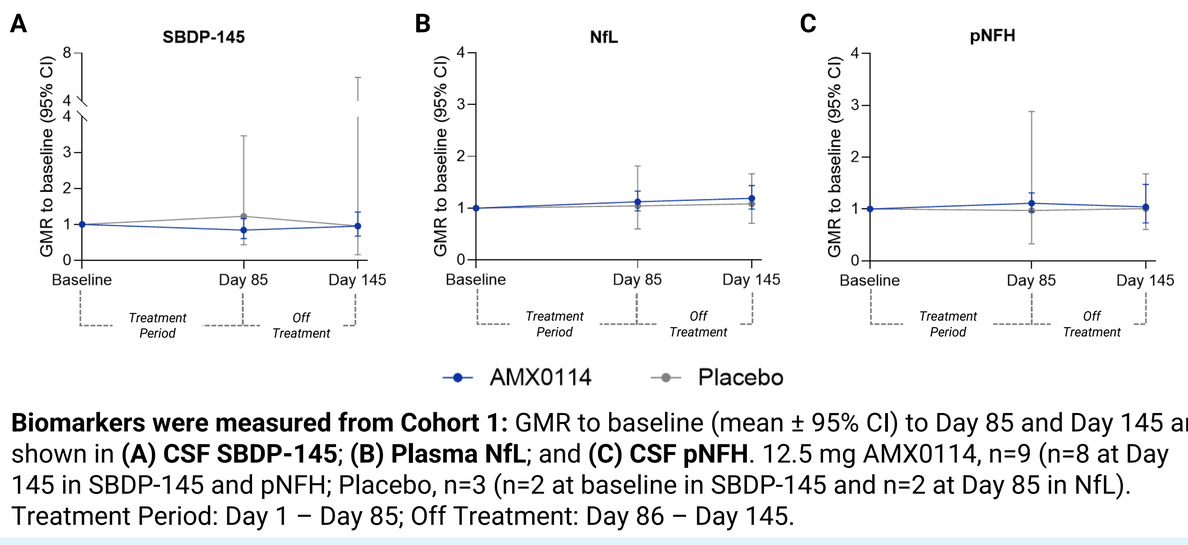
Cohort 1 Safety Data Supports Continued Evaluation[12]

	AMX0114 (12.5 mg) (n=9) **n** (%)	Placebo (n=3) **n** (%)
Any Treatment-Emergent Adverse Event (TEAE)	**9** (100%)	**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*)	**6** (67%)	**2** (67%)
Nervous System Disorders (*severe to fatal*)	**0**	**0**
General/Admin Site Conditions (*mild to moderate*)	**5** (56%)	**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 and were **more frequent** than drug-related events
- **No drug-related SAEs or serious neurologic AEs reported**

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.

No Biomarker Change With Lowest Dose of AMX0114



Biomarkers were measured from Cohort 1: GMR to baseline (mean ± 95% CI) to Day 85 and Day 145 are shown in **(A) CSF SBDP-145**; **(B) Plasma NfL**; and **(C) CSF pNFH**. 12.5 mg AMX0114, n=9 (n=8 at Day 145 in SBDP-145 and pNFH; Placebo, n=3 (n=2 at baseline in SBDP-145 and n=2 at Day 85 in NfL). Treatment Period: Day 1 – Day 85; Off Treatment: Day 86 – Day 145.

Conclusions

- No drug-related SAEs or serious neurological AEs were reported in Cohort 1.
- Biomarker levels remained near baseline within the time course, with no consistent or sustained changes observed at the lowest dose level (12.5 mg).
- Findings are not unexpected at this dose and timeframe and may reflect either insufficient exposure or duration. The safety and tolerability profile supports continued evaluation of higher dose levels.
- Cohort 2 is fully enrolled, Cohort 3 is enrolling, and study is ongoing.

Scan to Learn More about the LUMINA Trial

AMX0114 has not been approved for use by any health authorities (including the EMA, FDA, PMDA, and Health Canada).

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Disclosures

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Contact Info: Lauren Kett, MD, PhD
Lauren_kett@amylyx.com

Abbreviations

SBDP-145, spectrin breakdown product 145; NfL, neurofilament light chain; pNfH, phosphorylated neurofilament heavy chain; *CAPN2,* calpain-2; ALS, amyotrophic lateral sclerosis; SVC, slow vital capacity; PK, pharmacokinetic; PD, pharmacodynamic; ALSFRS-R, ALS Functional Rating Scale-Revised; TEAE, treatment-emergent adverse events; LP, lumbar puncture; CSF, cerebrospinal fluid; GMR, geometric mean ratio; ULN, Upper Limit of Normal ; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; INR, International Normalized Ratio; aPTT, Activated Partial Thromboplastin Time; CI, confidence interval