AMX0035

March 30, 2022

Amylyx Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee

Introduction

Justin Klee and Joshua Cohen

Co-CEOs and Co-Founders

Amylyx Pharmaceuticals

Establishing Effectiveness in ALS

"The statutory standards for effectiveness apply to drugs developed for ALS, just as the standards apply for all other drug development. However, FDA has also long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious disease with unmet medical needs, while preserving appropriate assurance of safety and effectiveness."

FDA Position, Combined FDA and Applicant Briefing Document, p. 12

CENTAUR Trial Developed and Conducted in Partnership with ALS Community

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute®

AMYLYX

CENTAUR Study Start — 2017

CENTAUR RCP Completed — 2019

CENTAUR Study End — 2021

2017 2018 2019 2020 2021

ALS Scientific Expert Contributions to CENTAUR

- Merit Cudkowicz, MD
  - Preeminent ALS researcher, CENTAUR Co-PI, senior clinical advisor
- Sabrina Paganoni, MD, PhD
  - Leading expert in ALS clinical trials, CENTAUR PI
- David Schoenfeld, PhD
  - Co-inventor of Finkelstein-Schoenfeld joint rank method; encouraged shared baseline mixed effects model for CENTAUR
- Jeremy Shefner, MD, PhD
  - Leading expert in ALS clinical trials, CENTAUR outcomes training

CENTAUR Trial Overview

Agenda

Clinical Trials in ALS

Jeremy Shefner, MD, PhD
Kemper and Ethel Marley Professor and
Chair of Neurology
Barrow Neurological Institute

Benefit / Risk

Jamie Timmons, MD
Head of Scientific Communications
Amylyx Pharmaceuticals

Clinical Perspective

Sabrina Paganoni, MD, PhD
Co-Director, Neurological Clinical Research Institute
and Healey & AMG Center for ALS
Massachusetts General Hospital
Associate Professor, Harvard Medical School

Additional Experts

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Head, Global Safety
Amylyx Pharmaceuticals

Suzanne Hendrix, PhD

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President
Mason Cardiac Consulting

Patrick Yeramian, MD, MBA

Chief Medical Officer
Amylyx Pharmaceuticals

Clinical Trials in ALS

Jeremy Shefner, MD, PhD

Kemper and Ethel Marley Professor and

Chair of Neurology

Barrow Neurological Institute

ALS Complex Disease to Study

- Patient population is heterogeneous
- Trial volunteers may drop out due to disease progression or burden of participation
- Historical dropout rate in ALS studies is 22%[1]
- There are no validated treatment-sensitive biomarkers

1. Atassi, 2013

2019 Airlie House Revised Consensus Guidelines and FDA ALS Guidance

- Inclusion criteria for prognostic enrichment and heterogeneity of disease progression
- Both function and survival regarded as important endpoints
- If function is assessed, the impact of missing data due to dropout and death should be accounted for
- Specific analysis plan not mandated

Revised Airlie House Consensus Guidelines, 2019; Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment. FDA Guidance for Industry, 2019

ALS Trial Designs Balance Need to Evaluate Both Function and Survival

- Enrolling participants early in disease course increases probability of survival throughout the study
- Other criteria contribute to increasing homogeneity of disease progression
- Inclusion criteria in CENTAUR study mandated
  - Short duration from symptom onset and requirement for diffuse disease prioritized rapid progression
- Open-label extension allowed longer term evaluation of mortality

ALS Functional Rating Scale-Revised (ALSFRS-R)

- Most commonly used primary outcome in ALS trials
- Global functional assessment across 4 motor domains
- Evaluators regularly trained and certified
  - Barrow Neurological Institute developed training and certification program
- Evaluators in CENTAUR trained and certified

The CENTAUR Study Employed ALSFRS-R Shared Baseline Mixed Effects Model

- Sensitive to therapeutic response especially when mortality events are sparse
- Effectively handles missing data
- Allows inclusion of important prognostic covariates
- Clinically meaningful endpoint used in many ALS trials

Standard of Care in ALS

- Riluzole approval
  - Survival benefit of 2 – 3 months
  - No observation of functional benefit
- Edaravone approval
  - 137-participant study run in Japan
  - 2.5 point benefit on ALSFRS-R
  - No survival benefit
- Standard of care use of riluzole and edaravone allowed in CENTAUR

Riluzole USPI, Edaravone USPI

In Summary

- Disease heterogeneity and overall progression rate can be addressed through choices in inclusion criteria
- Similarly, inclusion criteria can maximize participant survival
- When a functional endpoint is employed as primary outcome, statistical analyses to evaluate the impact of missing data due to dropout or death should be included
- Effective use of the ALSFRS-R requires uniform training and certification
- It is imperative that Standard of Care is provided to all participants

Benefit / Risk

Jamie Timmons, MD

Head of Scientific Communications

Amylyx Pharmaceuticals

Evidence Supports Positive Benefit / Risk for AMX0035

- Adequate, well-controlled clinical trial
- Significant functional benefit
- ITT overall survival benefit
- Generally safe and well-tolerated

CENTAUR Study Design and Execution

Adequate, well-controlled clinical trial

Significant functional benefit

ITT overall survival benefit

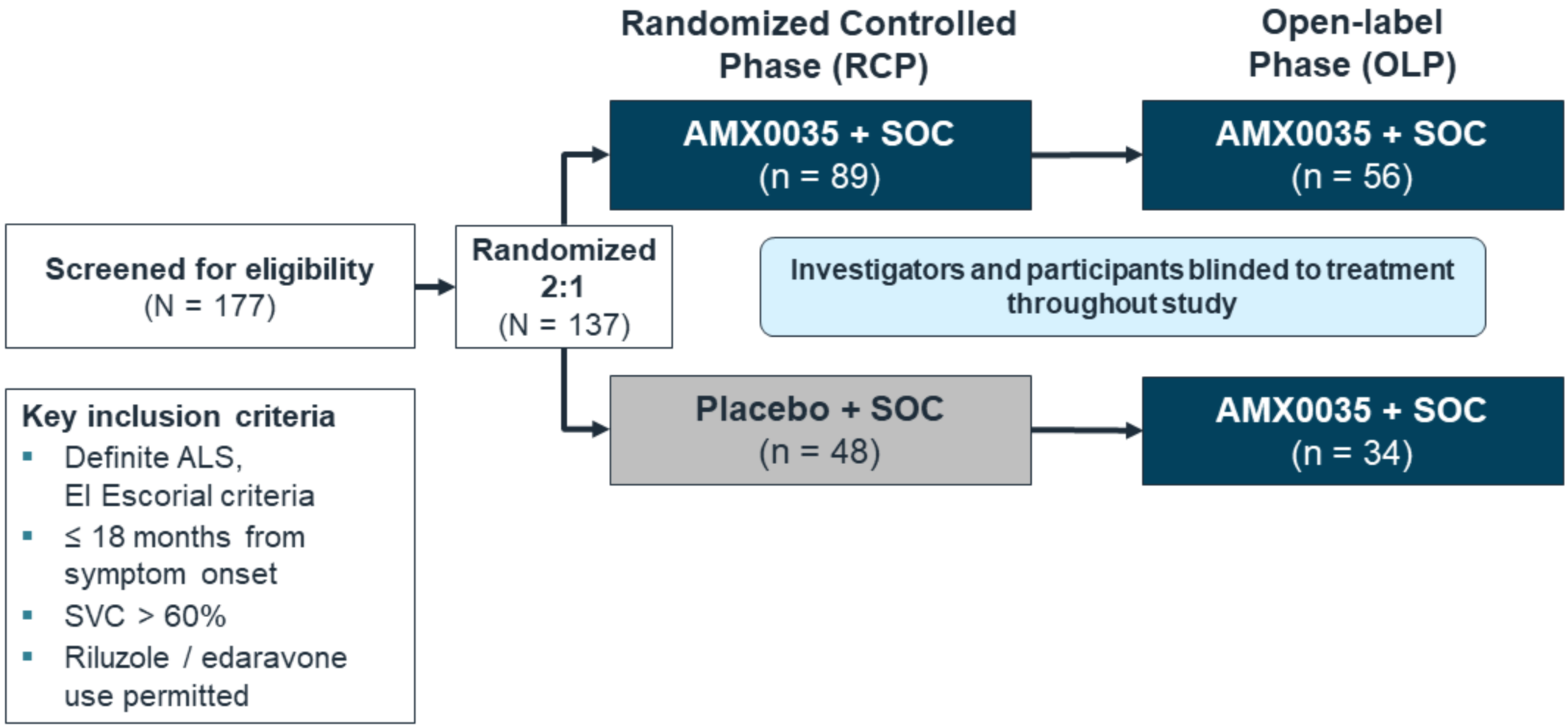
Generally safe and well-tolerated

CENTAUR Design Aligns with Best Practices in ALS Clinical Trials

Best Practice	CENTAUR Trial Design
Inclusion Criteria Address Disease Heterogeneity and Study Objectives	▪ Used inclusion criteria to allow measurement of function in randomized controlled phase
Uniform Training and Certification for ALSFRS-R	▪ ALSFRS-R evaluated in well-established and standardized manner
Appropriate Primary Endpoint and Analysis Methods	▪ ALSFRS-R analyzed using shared baseline, linear, mixed effects model, which accurately assesses treatment differences in studies with few mortality events ▪ Sensitivity analyses additionally accounted for missing data due to dropouts and death
Standard of Care Imperative	▪ AMX0035 benefit tested on top of standard of care

CENTAUR Study Design Had Two Phases

Multi-center Study, 25 US Centers



Randomization Implementation Problem Corrected Early, Did Not Impact Results

Analysis	AMX0035 + SOC n	AMX0035 + SOC Estimate (SE)	Placebo + SOC n	Placebo + SOC Estimate (SE)	Difference (95% CI)
Primary Outcome ALSFRS-R Total	87	**29.1** (0.8)	48	**26.7** (1.0)	**2.3** (0.2, 4.5)
Analysis excluding participants impacted by randomization error	71	**28.1** (0.9)	39	**25.6** (1.1)	**2.5** (0.1, 5.0)

mITT population

Participants and Investigators Blinded Throughout CENTAUR

- Taste
  - Placebo taste matched to AMX0035
- GI adverse events
  - Generally mild
  - Similar overall incidence between AMX0035 (66%) and placebo (63%)
- Exit questionnaire performed
  - Neither study investigators nor participants able to guess treatment assignment
- Blind maintained through entirety of both randomized and open-label phases

Limited Number of Deaths in CENTAUR Validate Primary Analysis Method Choice

- Few deaths during randomized controlled phase
  - 5 (6%) on AMX0035
  - 2 (4%) on placebo
- CENTAUR used shared baseline, linear, mixed effects model
  - Sensitive estimate of treatment effect
  - Accounted for missing data
  - Allowed inclusion of important prognostic covariates
  - Clinically meaningful endpoint

AMX0035 Impact on Function

Adequate, well-controlled clinical trial

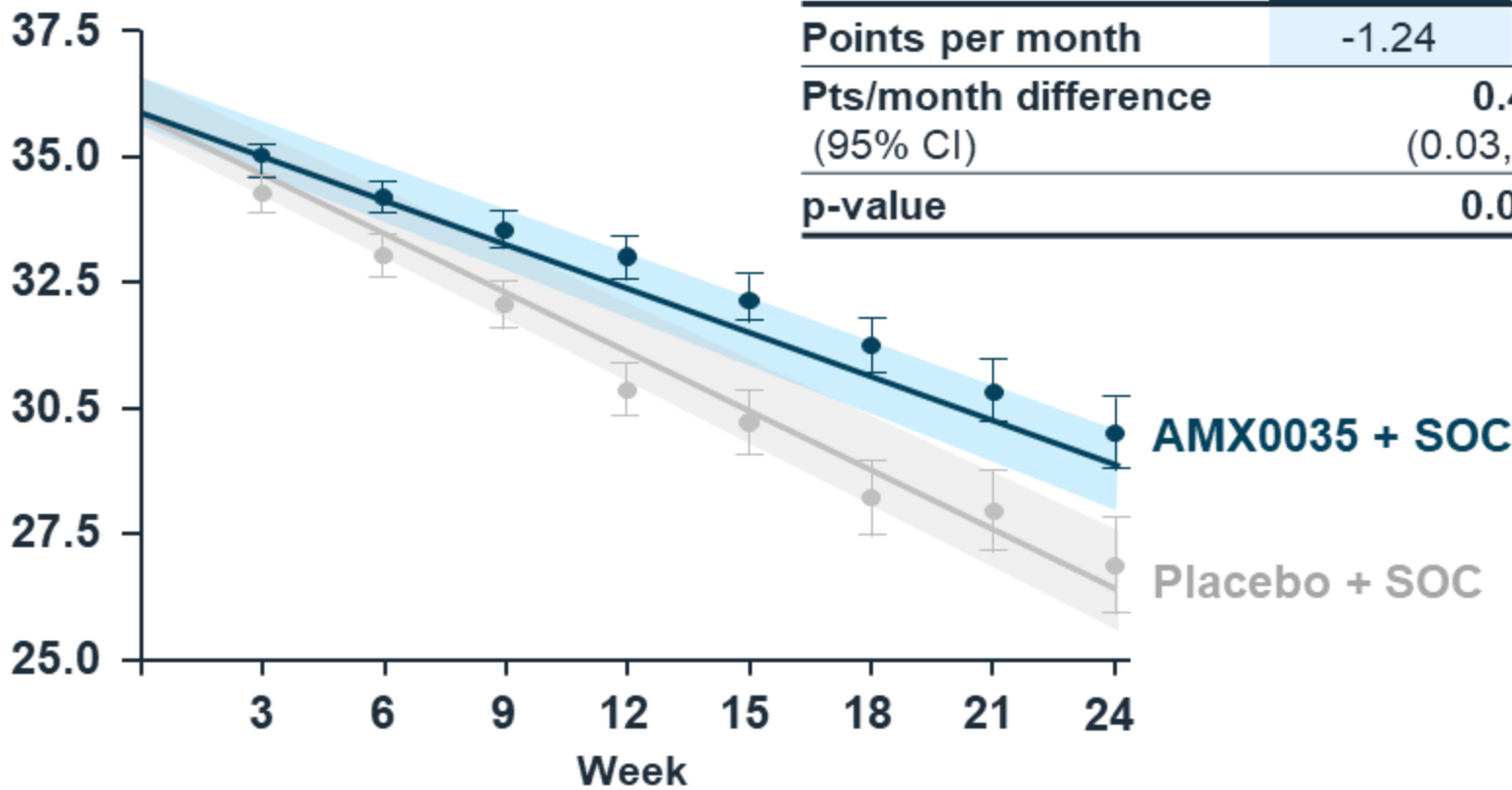
Significant functional benefit

ITT overall survival benefit

Generally safe and well-tolerated

AMX0035 Met Primary Endpoint 25% Slower Decline in Function

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Points per month	-1.24	-1.66
Pts/month difference (95% CI)	0.42 (0.03, 0.81)	
p-value	0.034	



No. of Participants									
AMX0035 + SOC	87	84	79	79	75	70	67	68	64
Placebo + SOC	48	48	44	44	44	43	39	38	37

mITT population

RCP Weeks 0-24: AMX0035 Met Primary Endpoint, Significant Benefit on Function

Endpoint at Week 24	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)	Difference (95% CI)	p-value
ALSFRS-R (SE)	**29.1** (0.8)	**26.7** (1.0)	**2.32** (0.2, 4.5)	**0.034**

mITT population

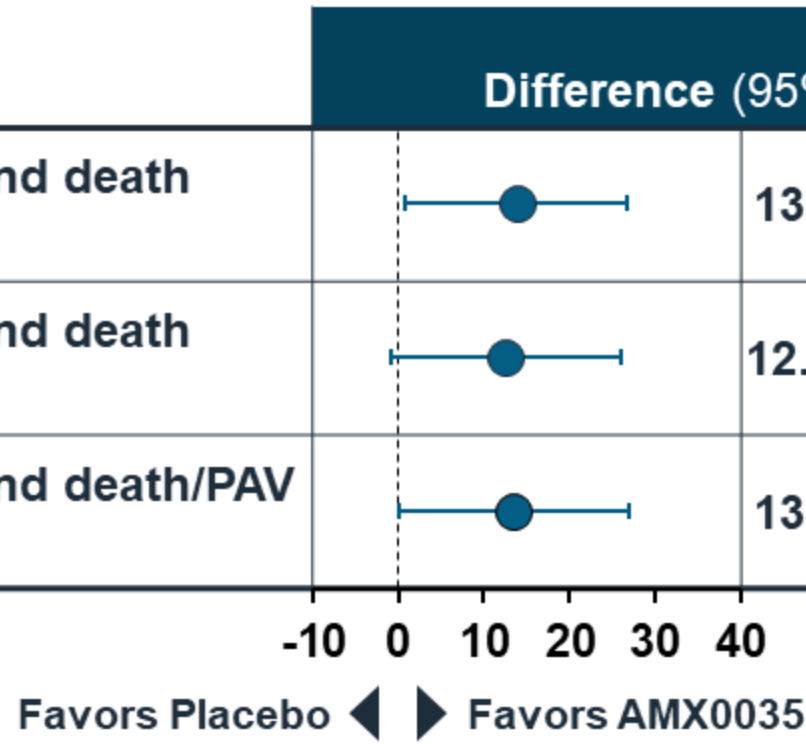
RCP Weeks 0-24: ALSFRS-R Results Consistent Across Sensitivity Analyses

Assumption Tested	ALSFRS-R Sensitivity Analysis	Difference (95% CI)	p-value
	Primary Outcome*	**2.3** (0.2, 4.5)	**0.034**
Shared baseline	Linear change from baseline	**2.9** (0.7, 5.2)	**0.010**
Linearity assumption	Separate means by visit change from baseline	**2.2** (0.2, 4.1)	**0.034**
Missing data	Multiple imputation for missing data*	**1.9** (0.1, 3.7)	**0.043**
Death	Left-censored*	**2.3** (0.2, 4.5)	**0.034**
	Worst-case = 0	**2.5** (0.0, 5.1)	**0.054**
Concomitant medications	Adjusted for time on edaravone during RCP*	**2.2** (-0.1, 4.4)	**0.056**
	Adjusted for time on riluzole during RCP*	**2.3** (0.2, 4.5)	**0.033**

*Prespecified analysis
mITT population

RCP Weeks 0-24: Joint Rank Analyses Accounting for Death Consistent

Analysis	Difference (95% CI)	p-value
Joint rank analysis for ALSFRS-R total score and death (last available data for deriving rank – mITT)	**13.9** (0.9, 26.8)	**0.038**
Joint rank analysis for ALSFRS-R total score and death (multiple imputation – ITT)	**12.6** (-0.8, 26.1)	**0.068**
Joint rank analysis for ALSFRS-R total score and death/PAV (multiple imputation – ITT)	**13.5** (0.1, 26.9)	**0.050**



AMX0035 Impact on Survival

Adequate, well-controlled clinical trial

Significant functional benefit

ITT overall survival benefit

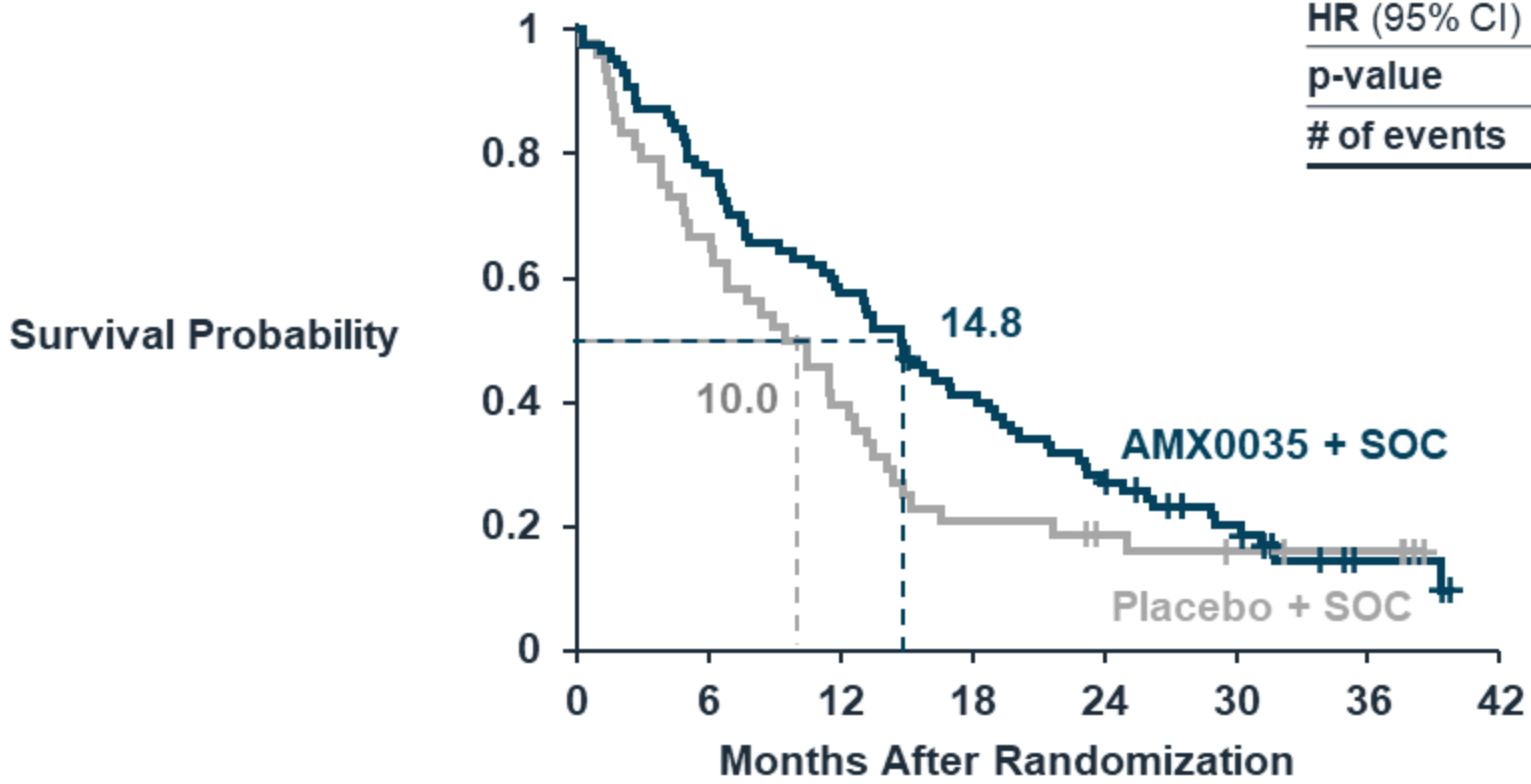
Generally safe and well-tolerated

Time-to-Event Outcomes

- Cut-off: March 2021 (last participant last visit in OLP)
- Comparison groups
  - Originally randomized to AMX0035 + SOC
  - Originally randomized to placebo + SOC
- Prespecified composite time to event endpoint
  - Death, hospitalizations, death equivalent

Prespecified mITT Composite Endpoint Met Overall Survival, Hospitalization, Death Equivalent

	Cox Regression Model
HR (95% CI)	**0.62** (0.4, 0.9)
p-value	0.023
# of events	112

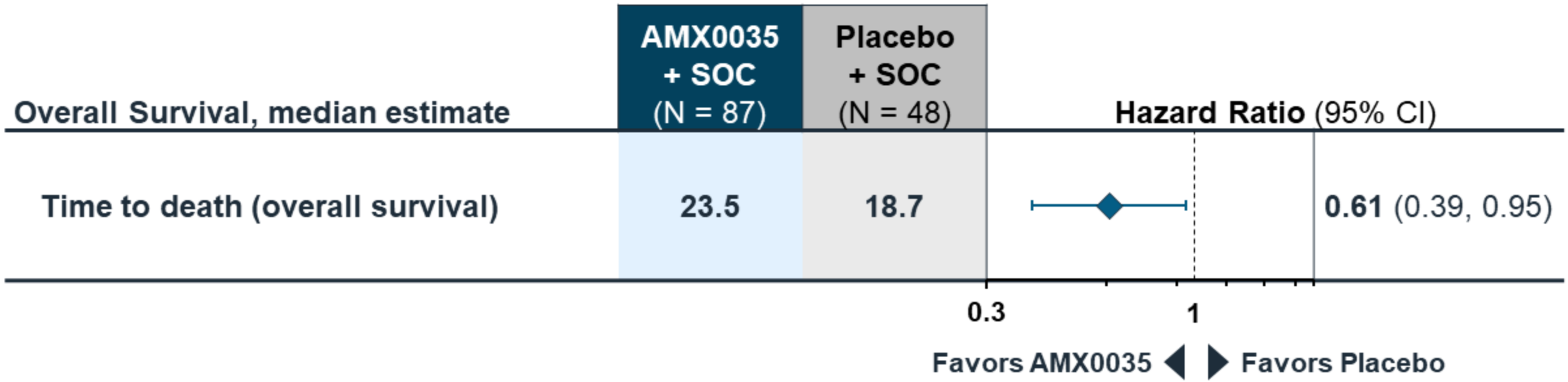


No. at Risk								
Originally Randomized to:	AMX0035 + SOC	87	67	50	35	23	13	3	0
	Placebo + SOC	48	32	19	10	7	5	4	0

Overall Survival Analysis Has Minimal Missing Data

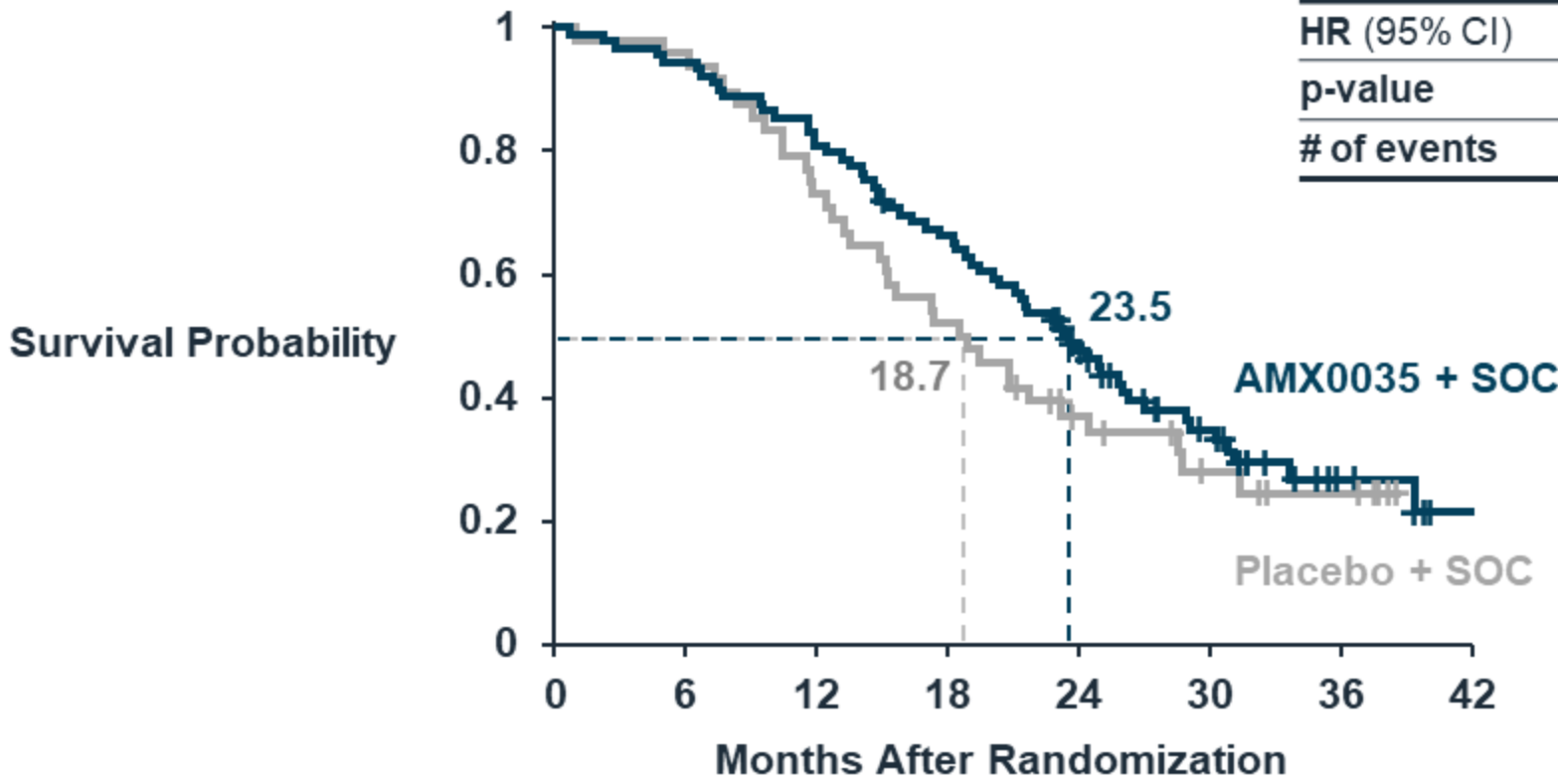
- Overall Survival (time to death)
- Comprehensive data capture – 136/137 participants
  - Clinic visits
  - Social Security death index
  - State and city records

Overall Survival Benefit in mITT Population



AMX0035 Results in Overall Survival Benefit in ITT Population

	Cox Regression Model
HR (95% CI)	**0.64** (0.4, 1.0)
p-value	0.045
# of events	94

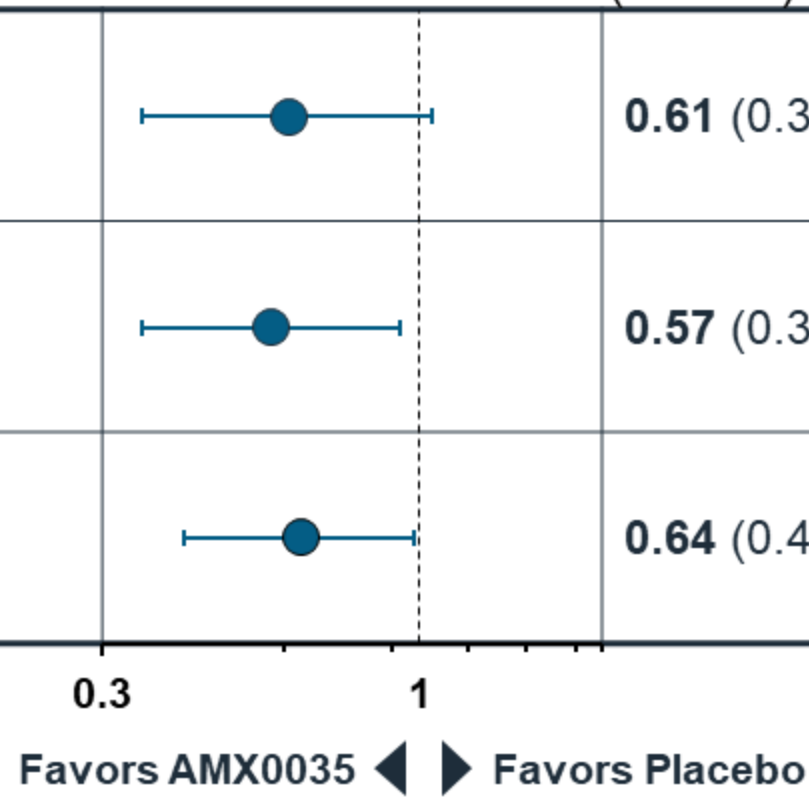


No. at Risk								
Originally Randomized to:	AMX0035 + SOC	89	84	72	58	38	21	6	1
	Placebo + SOC	48	46	35	25	14	8	5	0

Post-hoc analysis

Overall Survival Benefit Consistent Across All Cut-Off Dates in ITT Population

Overall Survival, median estimate	AMX0035 + SOC (N = 89)	Placebo + SOC (N = 48)	Number of Events	Hazard Ratio (95% CI)
February 29, 2020	23.8	20.8	58	**0.61** (0.35, 1.05)
July 20, 2020	25.8	18.9	72	**0.57** (0.35, 0.93)
March 1, 2021	23.5	18.7	94	**0.64** (0.41, 0.98)



Post-hoc analysis

AMX0035 Safety and Tolerability

Adequate, well-controlled clinical investigation	Significant functional benefit	ITT overall survival benefit	**Generally safe and well-tolerated**

AMX0035 Well-Tolerated with Favorable Safety Profile

- AEs and deaths balanced between treatment and placebo arms
- GI events with AMX0035 more frequent in first 3 weeks
- Fewer SAEs with AMX0035 and most related to ALS progression
- More AEs leading to drug withdrawal with AMX0035 related to GI symptoms
- Most AEs mild or moderate and manageable

AMX0035 Benefit / Risk

Adequate, well-controlled clinical trial

Significant functional benefit

ITT overall survival benefit

Generally safe and well-tolerated

Positive Benefit / Risk

Evidence Supports Positive Benefit / Risk for AMX0035

Benefits

- Benefit on both function and survival in rare, fatal disease with high unmet need
- Prespecified primary efficacy endpoint met
- Multiple sensitivity analyses support primary result
- Favorable safety profile

Risks

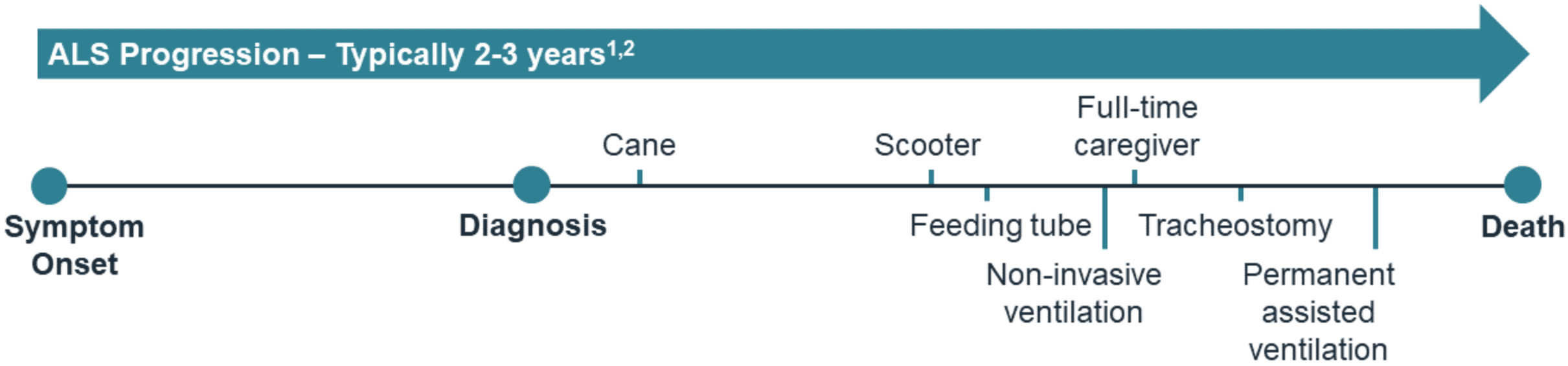
- GI events, generally mild and transient

Clinical Perspective

Sabrina Paganoni, MD, PhD

Co-Director, Neurological Clinical Research Institute and
Healey & AMG Center for ALS
Massachusetts General Hospital
Associate Professor, Harvard Medical School

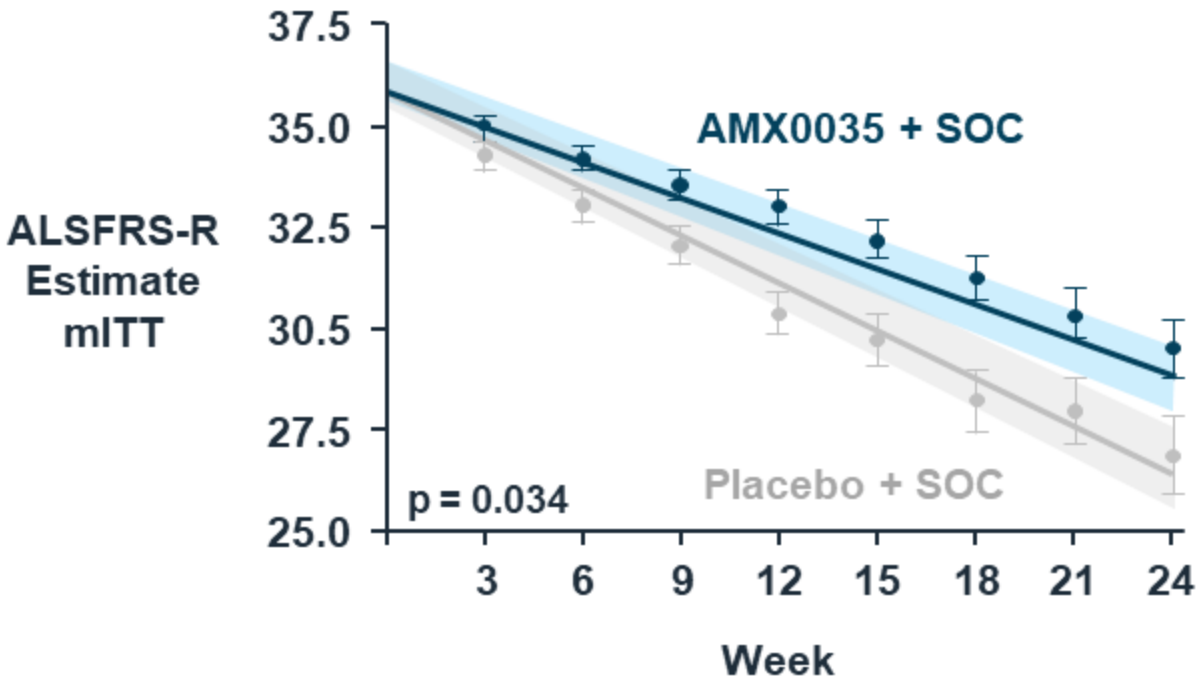
ALS Is Fast Progressing and Universally Fatal



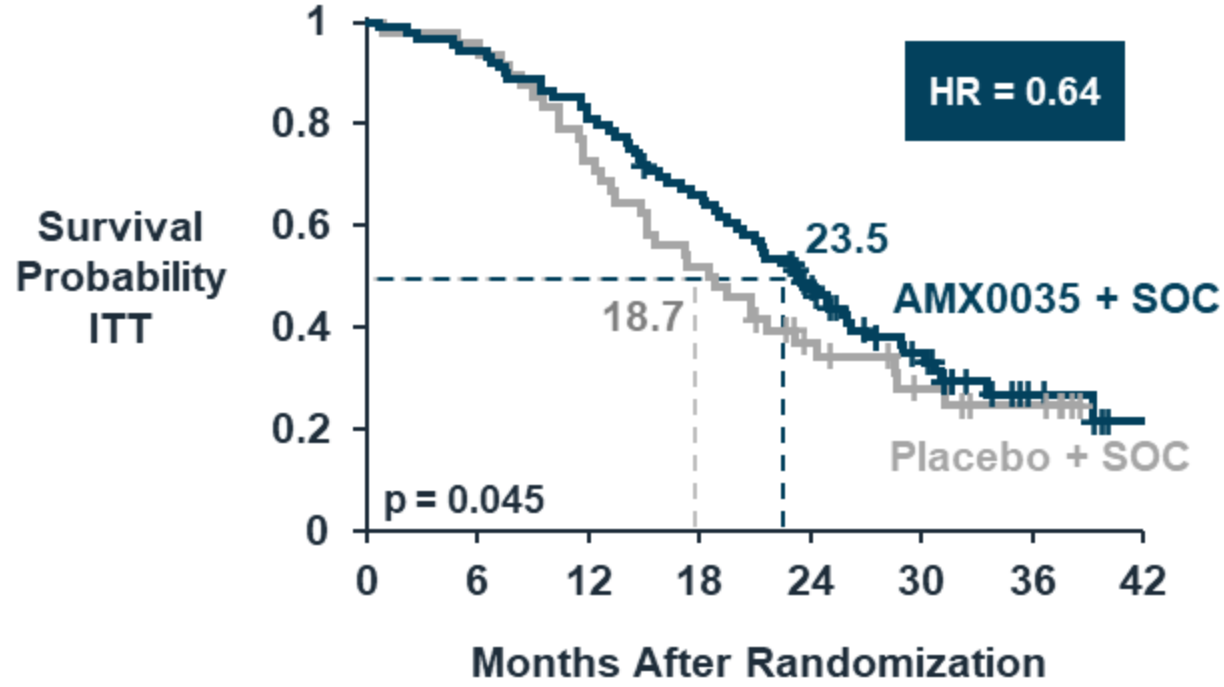
1. Paganoni, 2014; 2. Chiò, 2009

Participants Randomized to AMX0035 Retained Function Longer and Lived Longer

25% Slower Decline in Function



4.8 Months Longer Median Survival



Positive Benefit / Risk Supports Use of AMX0035

- Based on strength of efficacy data, benefit of AMX0035 is clear
- Based on favorable safety profile, risk of AMX0035 is low

- Greatest risk is delaying access to AMX0035

AMX0035

March 30, 2022

Amylyx Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee

BACK-UP SLIDES

PHOENIX: Study Design

Screen for eligibility

Randomization 3:2
(N = ~600)

AMX0035 + SOC

Placebo + SOC

Key inclusion criteria:

- Definite ALS or clinically probable ALS, El Escorial criteria
- < 24 months from symptom onset
- SVC ≥ 55%
- Riluzole / edaravone use permitted

Recruiting in 12 countries:

- ~55 Sites
- ~600 participants (Europe ≈ 400, US ≈ 200)

PHOENIX: US Sites by State

- **AZ:** Barrow Neurological Institute
- **CA:** University of Southern CA; University of CA Irvine; CA Pacific Medical Center Research Institute
- **CO:** Neurosciences Center - Anschutz
- **FL:** University of Florida; University of South Florida
- **GA:** Emory University; Augusta University Neuroscience Center
- **IL:** Northwestern University
- **MD:** Johns Hopkins University School of Medicine Outpatient Center
- **MA:** Healey and AMG Center for ALS Research at Massachusetts General Hospital; University of Massachusetts
- **MN:** Hennepin Healthcare Research Institute
- **MO:** Washington University School of Medicine
- **NE:** Somnos Clinical Research
- **NJ:** Rutgers University
- **NY:** Columbia University
- **NC:** University of NC Chapel Hill; Wake Forest University Health Sciences
- **OH:** The Ohio State University
- **PA:** University of Pennsylvania; Lewis Katz School of Medicine at Temple University
- **TX:** Austin Neuromuscular Center; Texas Neurology
- **VA:** Virginia Commonwealth University
- **WA:** Swedish Neuroscience Institute; University of Washington

PHOENIX: European Sites by Country

- 11 countries, 40 sites
- Belgium (1)
- France (7)
- Germany (7)
- Ireland (1)
- Italy (8)
- The Netherlands (1)
- Poland (2)
- Portugal (1)
- Sweden (2)
- United Kingdom (5)
- Spain (5)

Baseline Characteristics Well-Balanced, Including Neurofilament Levels

- Baseline NF levels were balanced between groups

	AMX0035 + SOC (N = 82)	**Placebo + SOC** (N = 46)
Baseline pNf-H (SD)	**345.7** (322.1)	**462.6** (432.9)

Weeks 0-48: Early Treatment with AMX0035 Associated with Slower Decline in Function

Treatment	RCP Weeks 0-24		OLP Weeks 24-48**	
	n	ALSFRS-R Change in Slope, Points per month (95% CI)	n	ALSFRS-R Change in Slope, Points per month (95% CI)
AMX0035 + SOC*	87	**-1.24** (-1.48, -1.00)	54	**-1.26** (-1.55, -0.97)
Placebo + SOC*	48	**-1.66** (-1.97, -1.35)	32	**-1.37** (-1.76, -0.98)

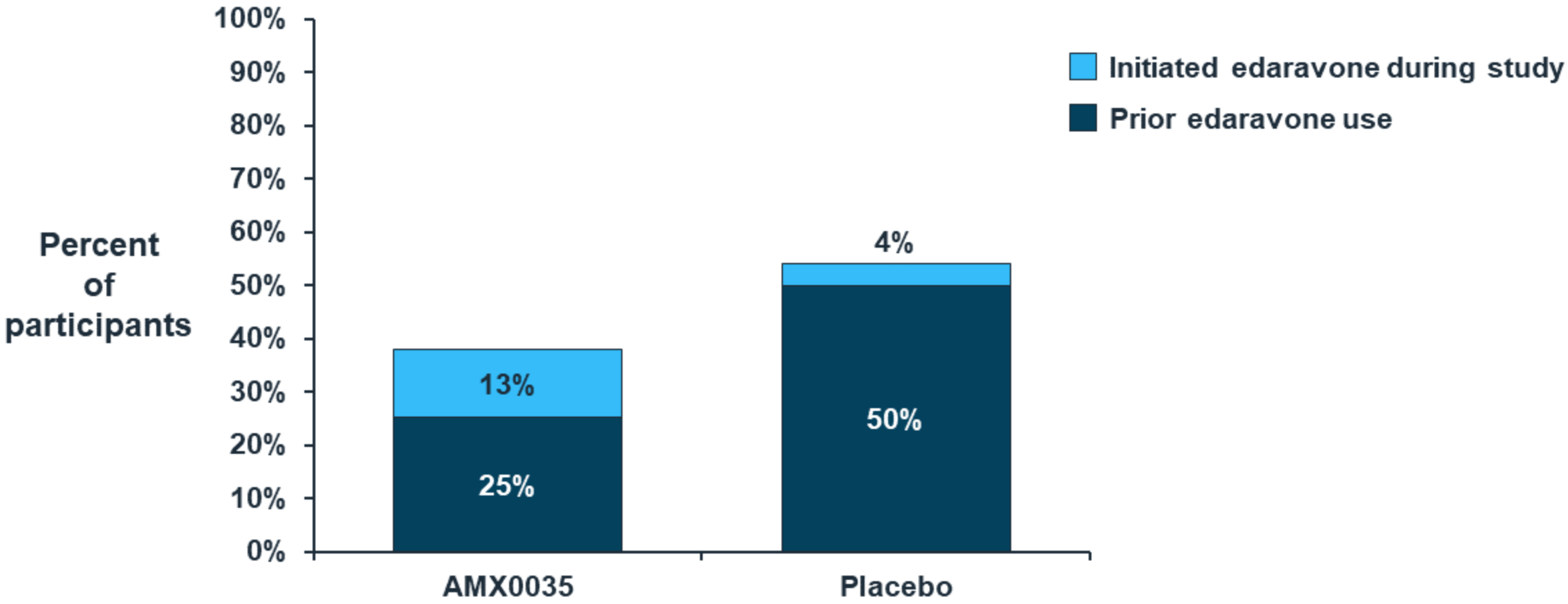
Linear shared baseline model
*Based on originally randomized treatment assignments
**Note: most participants in placebo group received AMX0035 during 24-48-week period

Longer Exposure to AMX0035 Associated with Longer Survival in Subgroup Analysis

Randomization Group	N	Mean Exposure to AMX0035 (Months)	Median Survival (Months, 95% CI)
Enrolled in Open-Label Phase			
AMX0035 + SOC	**56**	**15.6**	**29.1** (24.4, NE)
Placebo + SOC	**34**	**7.5**	**20.8** (17.2, 27.0)
Did Not Enroll in Open-Label Phase			
AMX0035 + SOC	**33**	**2.7**	**17.4** (14.6, 22.8)
Placebo + SOC	**14**	**0**	**15.2** (12.4, 24.9)

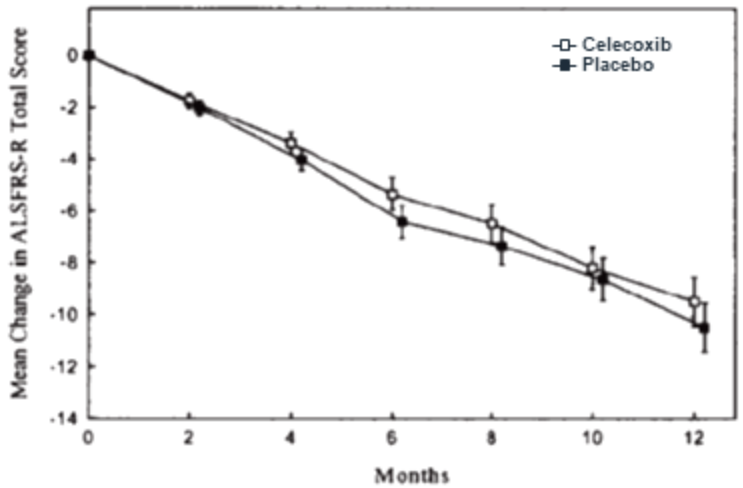
NE = Not Estimable

Edaravone Initiation During Study (mITT)

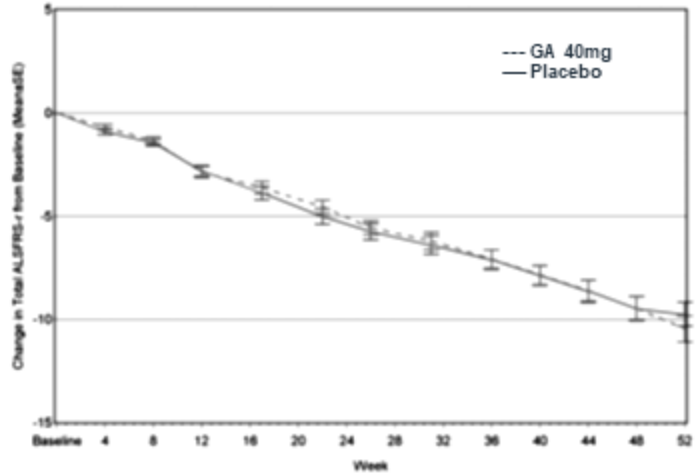


Decline in ALSFRS-R Over Time Is Linear

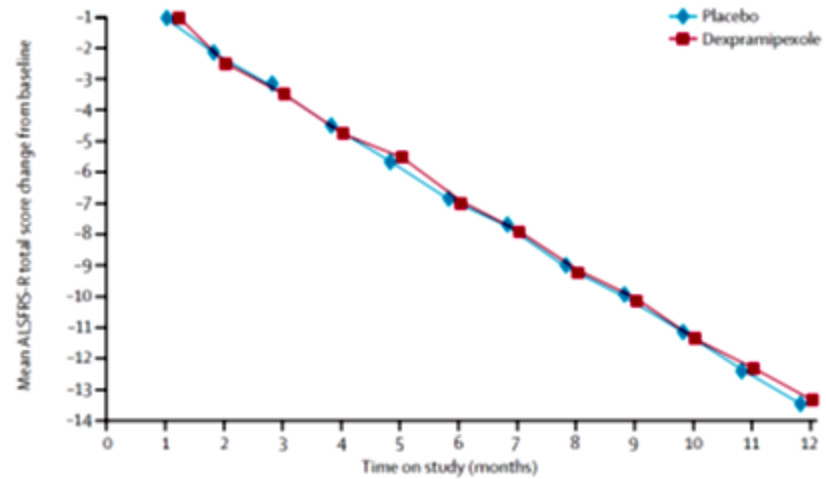
Celecoxib:
ALSFRS-R 43-33[1]



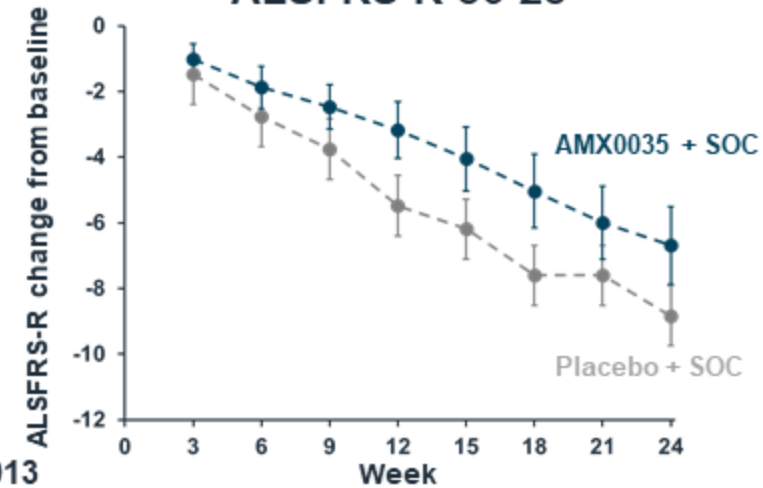
Copaxone:
ALSFRS-R 38-28[2]



Dexpramepexole:
ALSFRS-R 38-26[3]



AMX0035:
ALSFRS-R 36-28

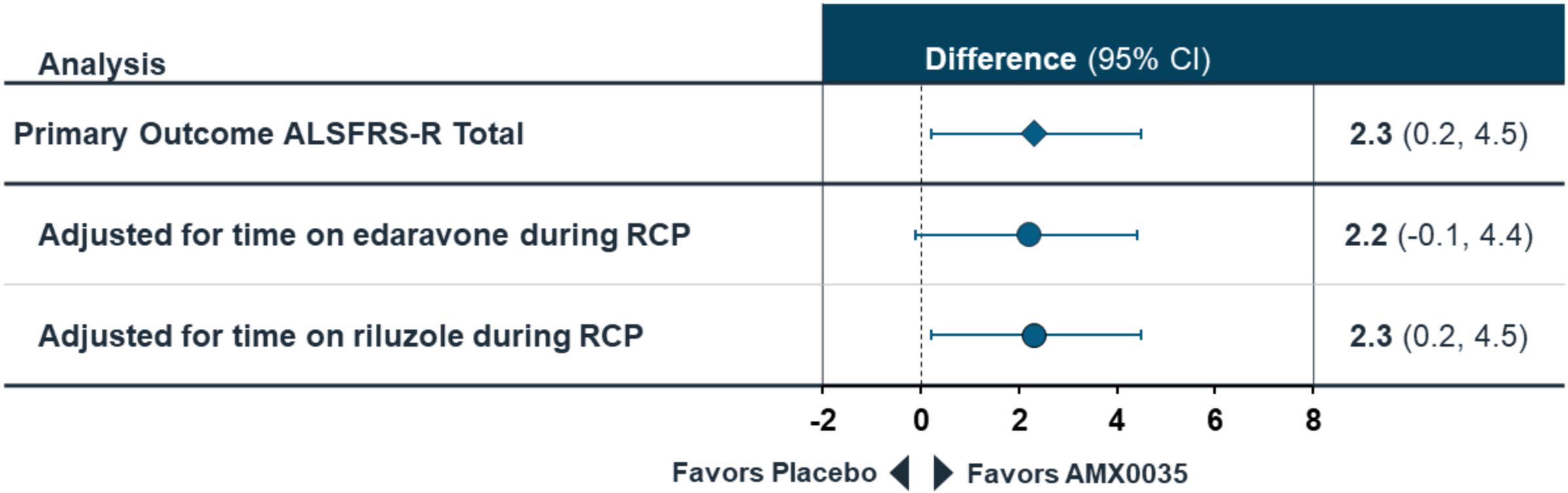


1. Cudkowicz, 2006; 2. Meninger, 2008; 3. Cudkowicz, 2013

RCP and OLP Prespecified Analysis Plans Finalized Before Unblinding

- October 14, 2019 – RCP SAP submitted
- November 5, 2019 – OLP SAP submitted
- November 26, 2019 – RCP unblinded to Amylyx
- April 1, 2020 – supplemental OS SAP submitted

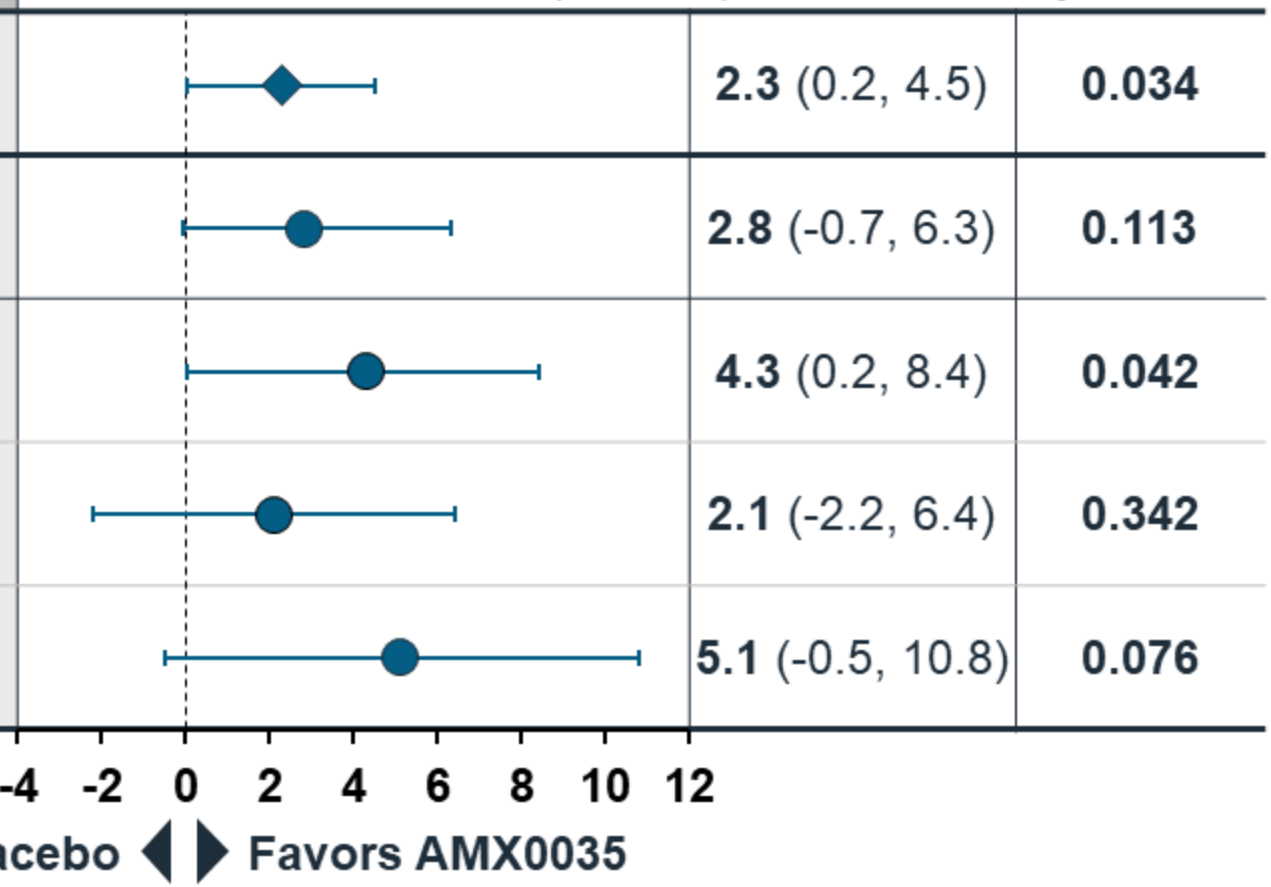
RCP Weeks 0-24: Function Benefit Maintained in Participants Taking Edaravone and Riluzole



mITT Population

RCP Weeks 0-24: Secondary Endpoints Support Primary Endpoint Results

Endpoint	AMX0035 + SOC N	AMX0035 + SOC Estimate (SE)	Placebo + SOC N	Placebo + SOC Estimate (SE)	Difference (95% CI)	p-value
ALSFRS-R Total	87	**29.1** (0.8)	48	**26.7** (1.0)	**2.3** (0.2, 4.5)	**0.034**
Total ATLIS	84	**39.1** (2.0)	47	**36.3** (2.2)	**2.8** (-0.7, 6.3)	**0.113**
Upper limb	85	**36.6** (2.3)	47	**32.4** (2.6)	**4.3** (0.2, 8.4)	**0.042**
Lower limb	85	**41.2** (2.4)	48	**39.1** (2.7)	**2.1** (-2.2, 6.4)	**0.342**
Slow Vital Capacity	87	**66.2** (2.3)	48	**61.1** (2.8)	**5.1** (-0.5, 10.8)	**0.076**



mITT Population

Survival – Prespecified Second Efficacy Outcome for Long-Term Follow-Up

Prespecified Hierarchy for Randomized Controlled Phase	Prespecified Hierarchy for Long-Term Follow-Up
ALSFRS-R rate of decline	ALSFRS-R rate of decline
ATLIS rate of decline	**Impact of AMX0035 on survival, hospitalization, and tracheostomies**
pNF-H rate of decline	Upper and Lower ATLIS scores rate of decline
SVC rate of decline	SVC rate of decline
Impact of AMX0035 on survival, hospitalization, and tracheostomies	Rate of progression on ALSFRS-R subdomains
Pharmacokinetics of AMX0035	Rate of progression on total ATLIS score
Results from exploratory TSPO PET substudy	