AMX0035

March 30, 2022

Amylyx Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee

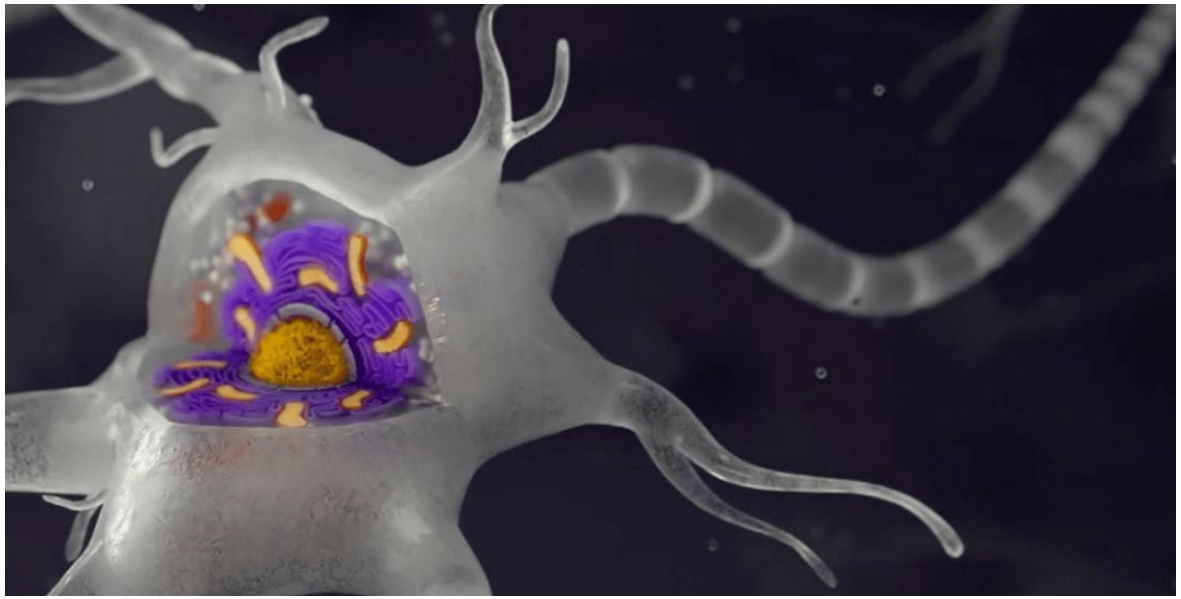
Introduction

Justin Klee and Joshua Cohen

Co-CEOs and Co-Founders

Amylyx Pharmaceuticals

Amyotrophic Lateral Sclerosis (ALS)
Rare, Progressive, Universally Fatal Disease

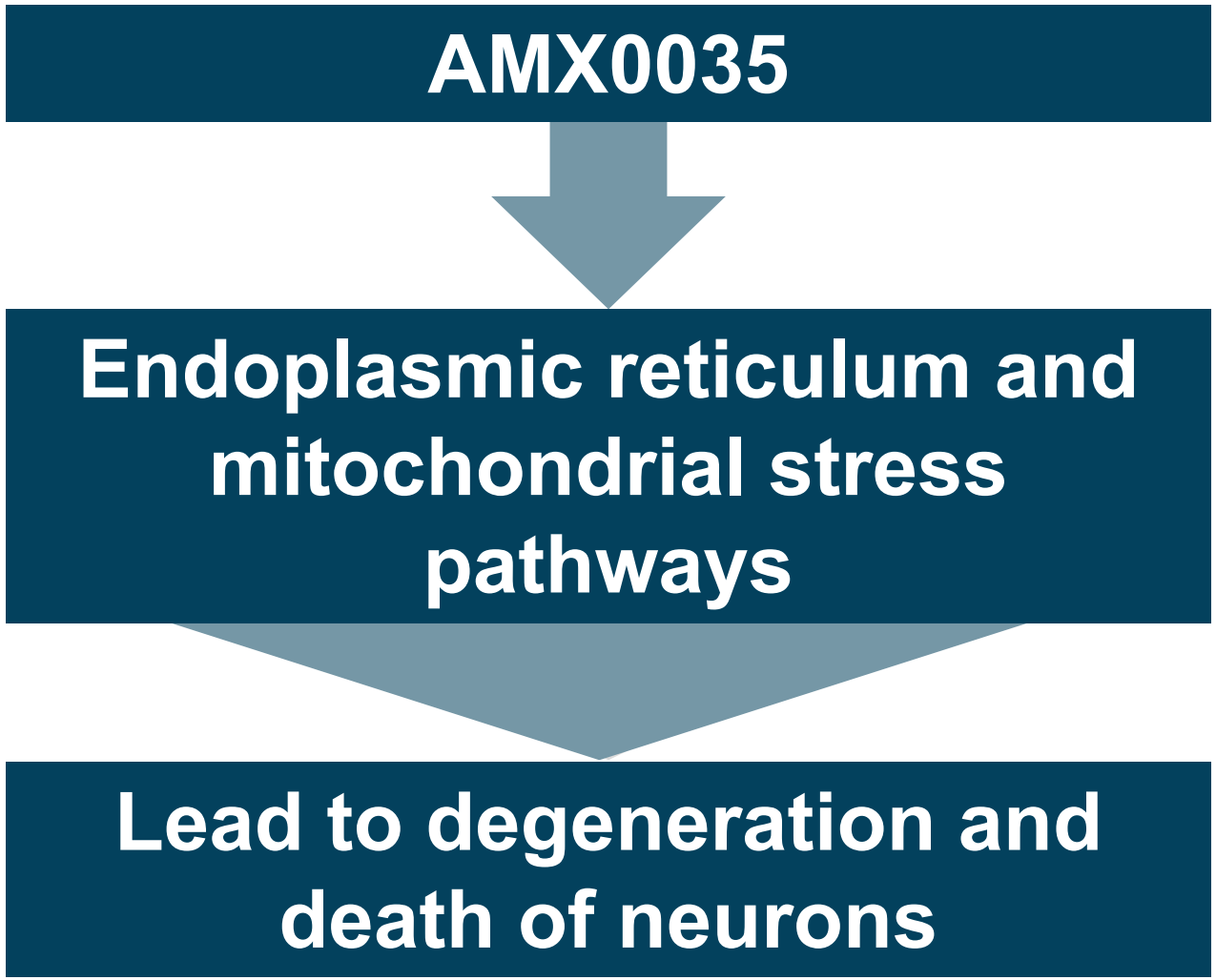


Degeneration and death of motor neurons

Rapid loss of basic function and death within few years

~ 500,000 Americans have died from ALS over past 80 years

Amylyx New Approach to Treating ALS

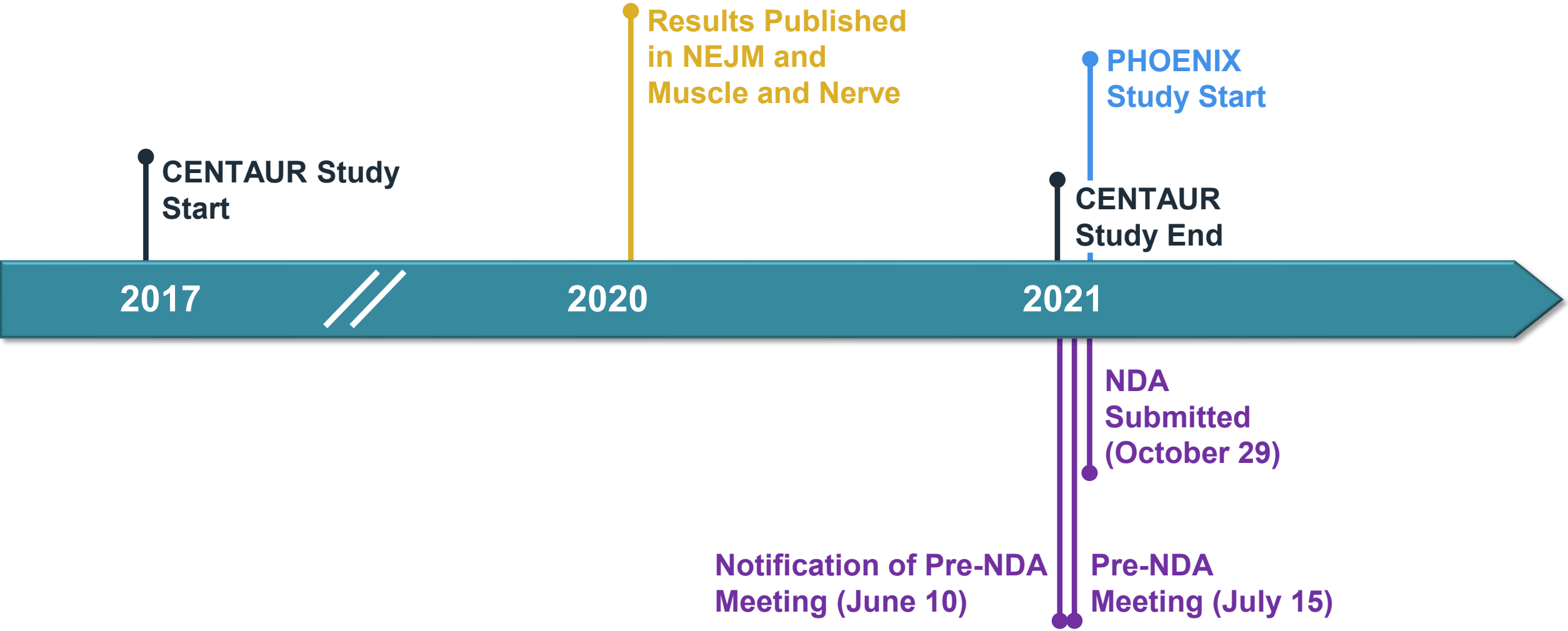


AMX0035 – Combination of Sodium Phenylbutyrate (PB) and Taurursodiol (TURSO)

- AMX0035 is indicated for the treatment of ALS

- Administered orally or via feeding tube
- Recommended starting dose: 1 sachet once daily for 1 to 21 days
- Maintenance dose: 1 sachet twice daily, morning and evening

AMX0035 Clinical Development and Regulatory History



CENTAUR Trial Overview

AMX0035 met primary endpoint

Slowed progression of functional decline

Statistically significant benefit on overall survival

Favorable safety profile

Numerically fewer SAEs

First treatment to show benefit on both function and survival in ALS

FDA Comments To Be Addressed

- Taste, GI AEs, blinding throughout OLP
- Primary analysis
- Survival methodology
- Statistical differences

Amylyx Commitment to ALS Community

- Continuing to study AMX0035 benefit in ALS
  - Another large placebo-controlled study
  - Already recruiting participants
  - Sites selected primarily outside US
  - Expected read-out in 2024
- Expanded access program in US for 250 participants

Agenda

Unmet Need	**Sabrina Paganoni, MD, PhD** Co-Director, Neurological Clinical Research Institute and Healey & AMG Center for ALS, Massachusetts General Hospital Associate Professor, Harvard Medical School
Endpoint Assessment in ALS	**Jeremy Shefner, MD, PhD** Senior Vice President Professor and Chair of Neurology Barrow Neurological Institute
Efficacy and Benefit / Risk	**Jamie Timmons, MD** Head of Scientific Communications Amylyx Pharmaceuticals
Clinical Perspective	**Sabrina Paganoni, MD, PhD**

Additional Experts

Shide Badri, MD, MPH
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Martin Bedigian, MD
CMO, Consultant

Marcelo Gutierrez, PhD
Head, Clinical Pharmacology
Amylyx Pharmaceuticals

Suzanne Hendrix, PhD
CEO, Consultant
Pentara Corporation

Jay Mason, MD
President
Mason Cardiac Consulting

Patrick Yeramian, MD, MBA
Chief Medical Officer
Amylyx Pharmaceuticals

Unmet Need

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 Has Broad Impact

> 29,000 adults in US living with ALS[1]

Lifetime risk[2]  1:440  1:350

Median onset of **55 years**, however ALS impacts broad age range, including young adults[3,4]

1. Nelson, 2021; 2. Ryan, 2019; 3. Chiò, 2013; 4. Brown, 2017

ALS Begins with Motor Neuron Degeneration and Death and Results in Loss of Function

Upper and Lower Motor Neuron Death

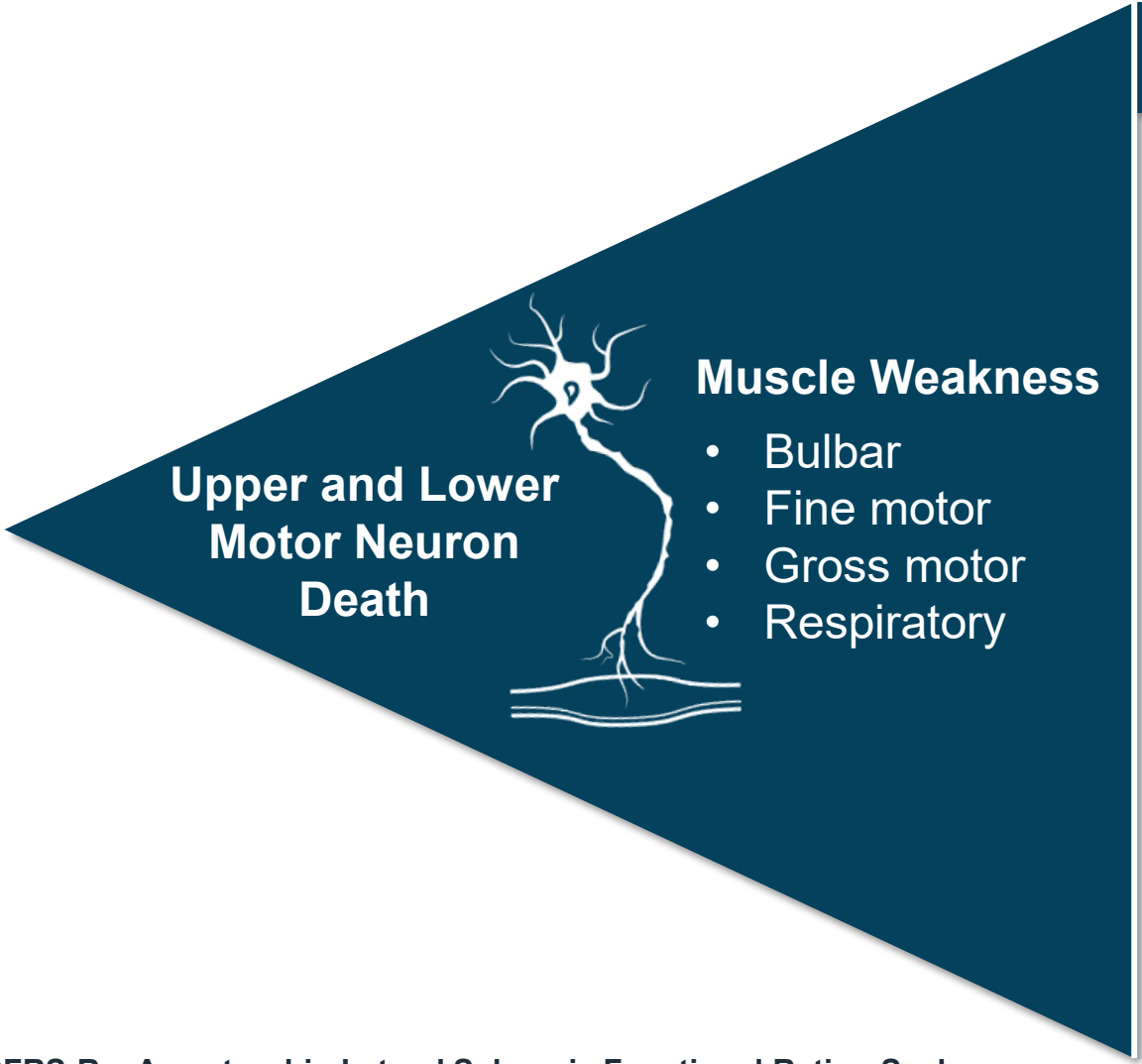
Muscle Weakness

- Bulbar
- Fine motor
- Gross motor
- Respiratory

Loss of Function

- Talking
- Eating
- Dressing
- Writing
- Walking
- Breathing

ALSFRS-R Widely Used to Measure Functional Decline in ALS



Loss of Function	ALSFRS-R

• Talking
• Eating
• Dressing
• Writing
• Walking
• Breathing
	• **Bulbar**
	  • Speech
	  • Salivation
	  • Swallowing
	• **Fine Motor**
	  • Handwriting
	  • Cutting food/using utensils
	  • Dressing and hygiene
	• **Gross Motor**
	  • Turning in bed
	  • Walking
	  • Climbing stairs
	• **Respiratory**
	  • Dyspnea
	  • Orthopnea
	  • Respiratory insufficiency

ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale

ALSFRS-R Measures Independence in Important Daily Functions

- Total of 48 points; 12 items rated on scale of 0-4

	SCORE				
	4	3	2	1	0
 **Example: Swallowing**	Normal eating	Early problems; occasional choking	Dietary consistency changes	Supplemental tube feedings needed	Only enteral or parenteral feeding

Cedarbaum, 1999

ALSFRS-R Categories Relevant to ALS

- Sensitive and reliable tool for assessing activities of daily living in ALS[1]
- Administered quickly in person or by phone[1,2]
  - Established equivalency of phone vs in-person testing[2]
- It has high inter-rater and test-retest reliability[1,2]
- Changes in ALSFRS-R scores predict survival and correlate with QoL measures[3,4]

1. Cedarbaum, 1999; 2. Kaufmann, 2007; 3. Kaufmann, 2005; 4. Wei, 2021

ALSFRS-R Predicts Survival

Variable	Hazard Ratio (95% CI)	p-value
Age at baseline, years	**1.02** (1.01, 1.04)	**0.01**
Male vs Female	**0.85** (0.53, 1.35)	**0.5**
Symptom duration, years	**0.74** (0.63, 0.87)	**< 0.001**
Total ALSFRS-R score	**0.93** (0.90, 0.96)	**< 0.001**
Forced Vital Capacity, % predicted	**0.99** (0.98, 1.01)	**0.3**
Riluzole use, ever vs never	**0.85** (0.54, 1.33)	**0.5**
Site of symptom onset		
Upper extremity	**1.00**	reference
Lower extremity	**1.17** (0.66, 2.07)	**0.6**
Bulbar	**1.81** (0.99, 3.33)	**0.05**
Respiratory	**6.52** (2.72, 15.60)	**< 0.001**

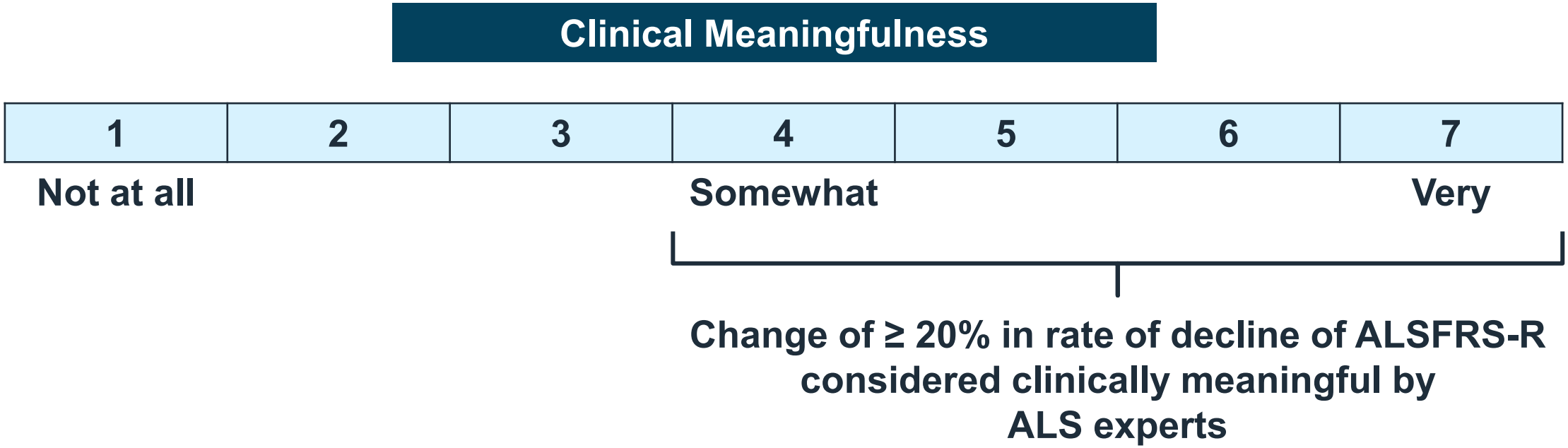
Kaufmann, 2005

ALSFRS-R Correlates with QoL Measures

Variable	Number	Health utility score median, (IQR)	p-value	EQ-VAS score median, (IQR)	p-value
Age of consent					
> 45	390	**0.74** (0.57, 0.88)	0.026	**70.0** (50.0, 80.0)	0.542
< 45	113	**0.80** (0.63, 0.91)		**70.0** (60.0, 80.0)	
Sex					
Male	319	**0.78** (0.58, 0.91)	0.055	**70.0** (50.0, 80.0)	0.221
Female	184	**0.73** (0.57, 0.87)		**70.0** (50.0, 80.0)	
Onset region					
Bulbar onset	62	**0.90** (0.80, 1.00)	< 0.001	**70.0** (60.0, 80.0)	0.019
Spinal onset	441	**0.73** (0.56, 0.86)		**70.0** (50.0, 80.0)	
ALSFRS-R score					
≥ 40	378	**0.80** (0.67, 0.91)	< 0.001	**70.0** (60.0, 80.0)	< 0.001
< 40	125	**0.53** (0.31, 0.68)		**55.0** (50.0, 70.0)	

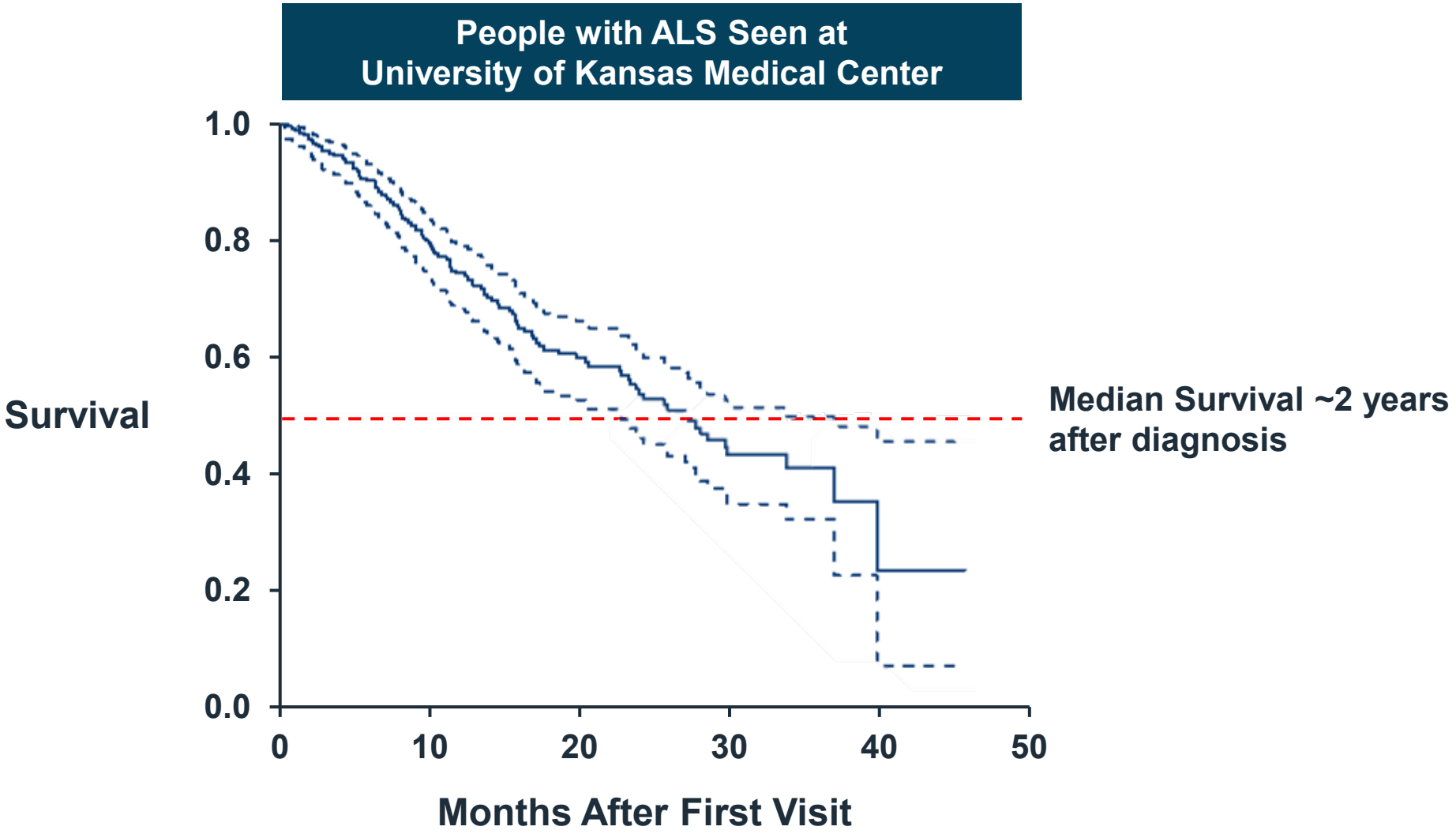
Wei, 2021

Change in ALSFRS-R Clinically Meaningful



Castrillo-Viguera, 2009

ALS Clock Short and Relentless



Karanevich, 2018

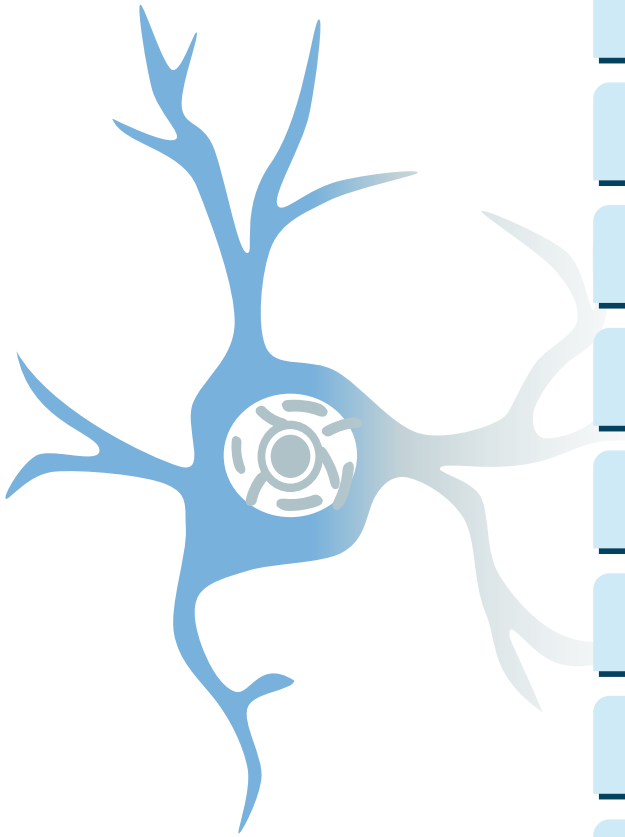
Clinically Meaningful Benefit Demonstrated by Median Overall Survival (OS) and Hazard Ratio (HR)

- ASCO guidelines specify 2.5 to 6 months improvement in median OS as clinically meaningful
- ASCO guidelines recommend HR as informative outcome in combination with median OS
  - Clinically meaningful overall survival benefit: HR ≤ 0.8

ASCO = American Society of Clinical Oncology

Ellis, 2014

ALS Is Multipathway Problem



- Genetic abnormalities[1,2]
- Oxidative stress[3-5]
- Axonal degeneration[6,7]
- Aberrant mRNA processing & transport[8,9]
- Neuroinflammation[10,11]
- Synaptic dysfunction[12,13]
- ER stress[2,14]
- Mitochondrial dysfunction[15,16]

Upper and Lower Motor Neuron Death

1. Chung, 2018; 2. Edenharter, 2018; 3. Chen, 2012; 4. Hardiman, 2017; 5. Cunha-Oliveria, 2020; 6. Fischer, 2007; 7. Brunden, 2017; 8. Liu, 2017; 9. La Rosa P, 2020; 10. Stephenson, 2018; 11. Liu, 2017; 12. Wishart, 2006; 13. Ling, 2020; 14. Lindholm, 2006; 15. Johri, 2012; 16. Manfredi, 2016.

Standard of Care in ALS Includes Multidisciplinary Approach

- Physical and occupational therapy
- Nutrition support (feeding tube)
- Breathing support (ventilator)
- Speech and assistive technology
- Palliative medicine and hospice

Paganoni, 2017

Only Two Approved Products for ALS in US

Riluzole

- Approved in 1995
- Blocks glutamatergic neurotransmission in CNS
- Survival ~2–3 months[1]
- No effect on function shown[1]

Edaravone

- Approved in 2017
- Antioxidant
- Slows functional decline[2]
- No survival benefit shown[3]

1. Riluzole FDA Label ; 2. Edaravone FDA Label; 3. Writing Group, 2017

Need Effective Treatments that Impact Both Function and Survival

- Limited current treatment options
- Clock already ticking by time of ALS diagnosis
- Need treatments that retain function and prolong survival

Endpoint Assessment in ALS

Jeremy Shefner, MD, PhD

Senior Vice President

Professor and Chair of Neurology

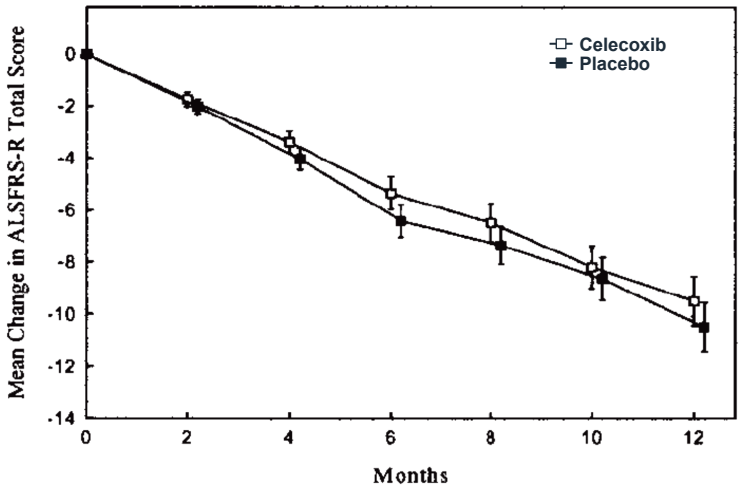
Barrow Neurological Institute

Experience in ALS Research

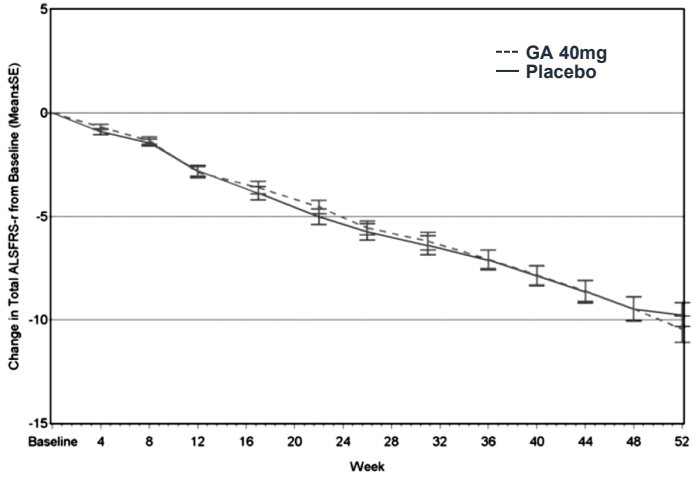
- 1996 – Cofounded Northeast ALS Clinical Trials Consortium
  - Largest consortium of academic centers performing ALS trials in world
- Executive committee or PI of multiple / multi-center ALS trials
- Research interests focus on development of functional biomarkers for ALS
- 2014 – Received Sheila Essey Award for ALS research

Decline in ALSFRS-R Over Time Is Linear

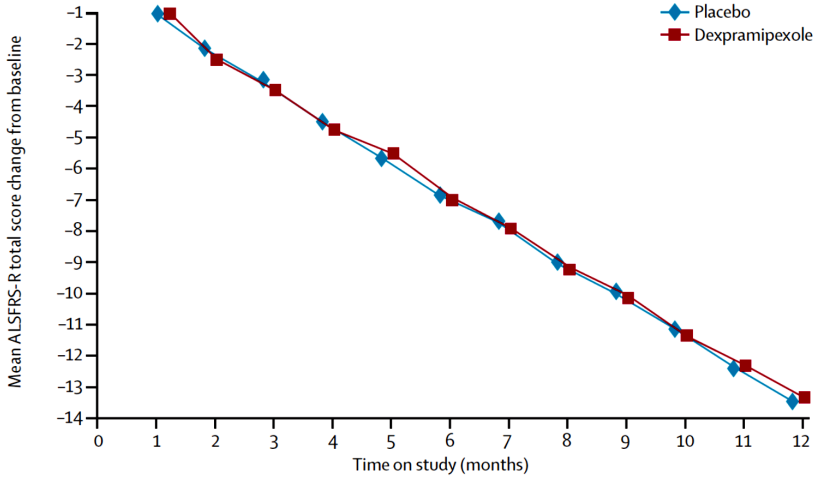
Celecoxib: ALSFRS-R 43-33[1]



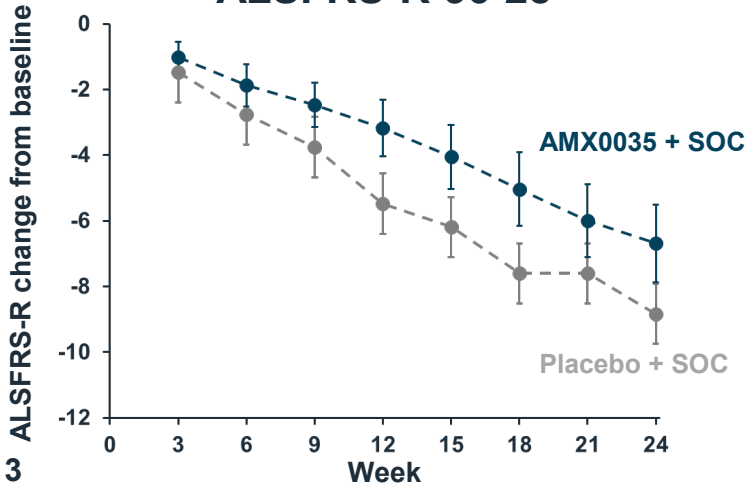
Copaxone: ALSFRS-R 38-28[2]



Dexpramepexole: ALSFRS-R 38-26[3]



AMX0035: ALSFRS-R 36-28



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

ALSFRS-R Shared Baseline Mixed Effects Model Most Appropriate Primary Analysis for CENTAUR

- Shared baseline, linear, mixed effects model of ALSFRS-R
  - Provides sensitive estimate of treatment effect
  - Effectively handles missing data
  - Allows inclusion of important prognostic covariates
  - Clinically meaningful endpoint used in many ALS trials
- Joint rank
  - Less sensitive when number of deaths expected low
  - Not designed to adjust for covariates
  - No robust methods for handling missing data
  - No intuitive clinical meaning, only p-value

Summary

- ALSFRS-R decline over time is linear in past ALS trials and appears to be linear in CENTAUR
  - Sensitivity analyses to test this assumption have not shown significant deviation
- Prespecified shared baseline, linear, mixed effects model chosen for primary outcome in CENTAUR appropriate
- Few deaths over 24 weeks, limiting utility of joint rank analysis

Efficacy and Benefit / Risk

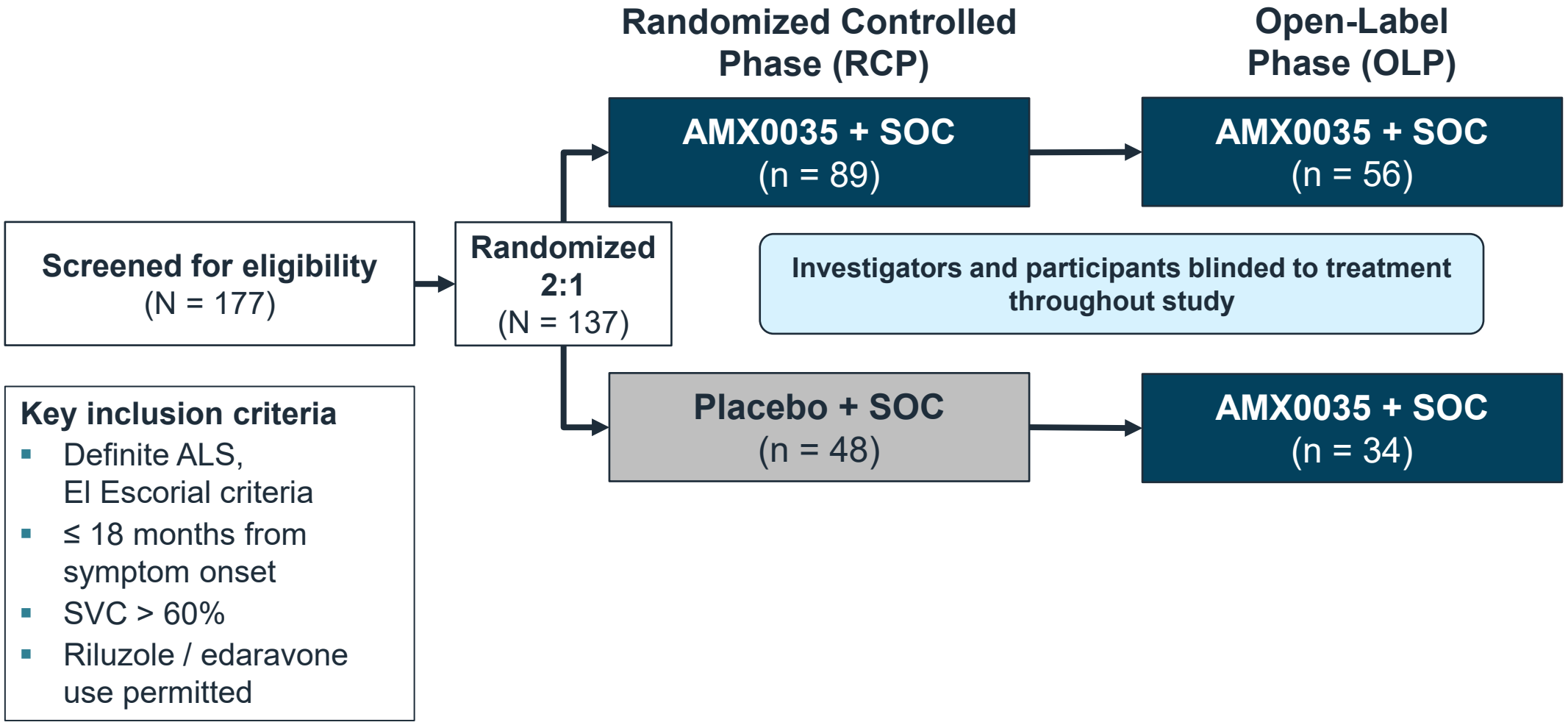
Jamie Timmons, MD

Head of Scientific Communications

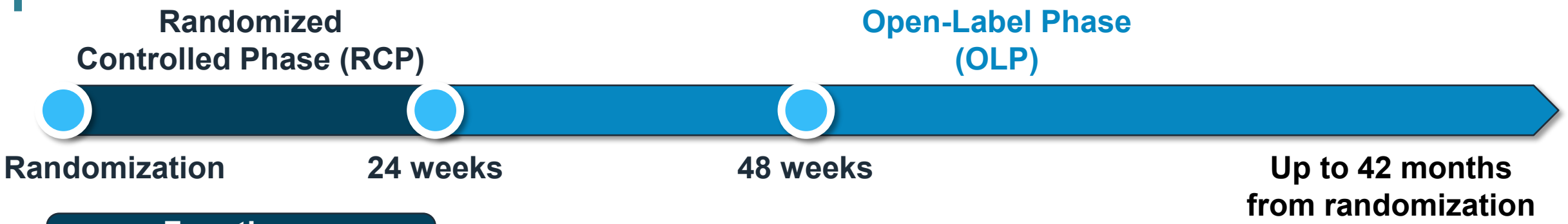
Amylyx Pharmaceuticals

CENTAUR Study Design Had Two Phases

Multi-center study, 25 US centers



Endpoints and Duration of Follow-Up Allowed for Robust Evaluation of AMX0035 Efficacy



Function – Primary Endpoint

Function – Extended Analysis

Key Secondary Endpoints

Key Secondary Endpoints – Extended Analysis

Overall survival, time to hospitalization, or death equivalent

Efficacy Endpoints Used Validated Tools

- Primary endpoint
  - Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R): function
- Key secondary endpoints
  - Accurate Test of Limb Isometric Strength (ATLIS): muscle strength
  - Slow Vital Capacity (SVC): respiratory function
- Time to events
  - Composite of and individual measures
    - Time to death (overall survival)
    - Time to first hospitalization
    - Time to death equivalent (tracheostomy or permanent assisted ventilation)

Randomization Error Occurred, Cause and Impact Thoroughly Investigated

- Kits shipped one by one after successful screening visits
- Early in study, unblinded statistician discovered that initial 18 study kits shipped were all active drug
  - Due to error at distribution center
  - 9 placebo kits shipped next
- Randomization ratio maintained with no unblinding and no further issues
- Sponsor not aware until two months after unblinding
  - No physicians or participants aware
- Sponsor initiated thorough investigation and consulted with external statisticians
  - Sensitivity analysis conducted showing no impact on primary outcome

Adverse Events and Study Drug Taste Unlikely to Result in Unblinding

- Taste
  - AMX0035 and placebo taste matched
- 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 at rate better than chance

Blind Maintained Through End of OLP

- Blind maintained through entirety of both randomized and open label phases of CENTAUR
- Sites emailed unblinded treatment information on October 15, 2021
  - OLP last participant last visit: March 1, 2021

Prespecified Hierarchies in Two Analysis Plans

Randomized Controlled Phase	Open-Label Phase
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	

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

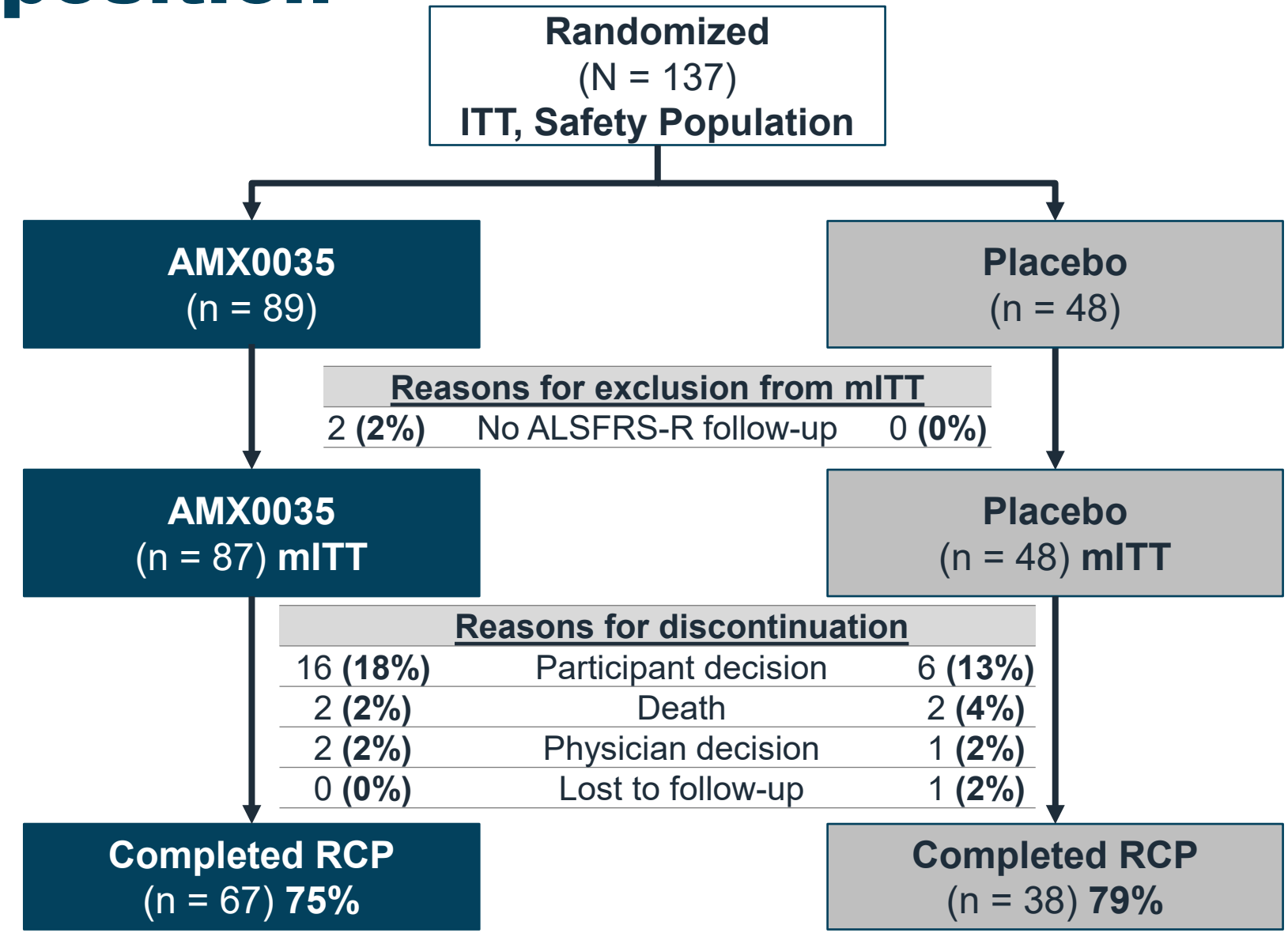
RCP: Sample Size Calculation

- Shared-baseline, mixed-effects analysis
- 2:1 randomization between treatment and placebo
- ~131 participants followed over 6 months
- 80% power
- 30% treatment effect
- One-sided alpha of 0.05

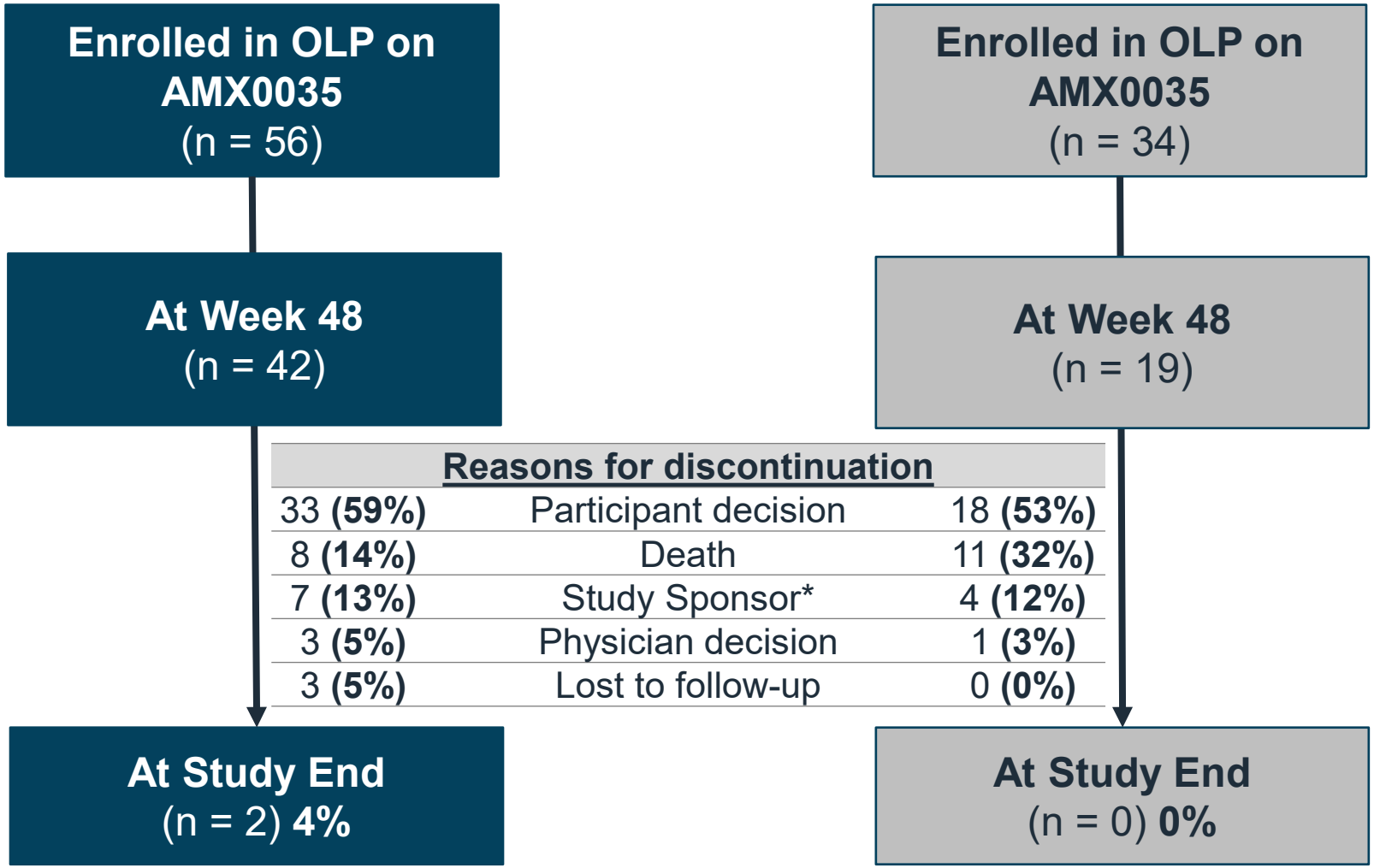
Prespecified Modified Intent to Treat (mITT) Efficacy Analysis Population

- Defined as all participants who
  - Received ≥ 1 dose of study drug
  - Had ≥ 1 post-baseline ALSFRS-R measurement
- mITT definition recommended by FDA
- Safety analyses used ITT population

RCP: Disposition



OLP: Disposition



*Participants moved to Extended Use Protocol

RCP Weeks 0-24: Demographics Balanced Between Groups

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Age (years), mean (SD)	**58** (10)	**57** (8)
Male (% participants)	**70%**	**67%**
Race		
White	**94%**	**96%**
Black / African American	**2%**	**2%**
Asian	**2%**	**2%**
Hispanic / Latino	**7%**	**2%**
BMI (kg/m^2), mean (SD)	**27** (4)	**26** (6)
United States (% participants)	**100%**	**100%**

RCP Weeks 0-24: Baseline Characteristics Generally Similar Between Groups

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Time Since ALS Diagnosis (months), mean (SD)	**5.9** (3.3)	**6.3** (3.2)
Time Since ALS Symptom Onset (months), mean (SD)	**13.5** (3.8)	**13.6** (3.6)
ALSFRS-R Total Score, mean (SD)	**35.7** (5.8)	**36.7** (5.1)
ATLIS Total Score (% predicted normal), mean (SD)	**57%** (20.1)	**54%** (20.9)
SVC (% predicted normal), mean (SD)	**84**% (15.9)	**84%** (18.2)
Pre-baseline ALSFRS-R slope (Del-FS), mean (SD)	**1.0** (0.4)	**0.9** (0.6)

RCP Weeks 0-24: Concomitant ALS Medication Use

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Baseline Edaravone or Riluzole Use	71%	88%
Edaravone Use	25%	50%
Riluzole Use	68%	77%

Prespecified Primary Model

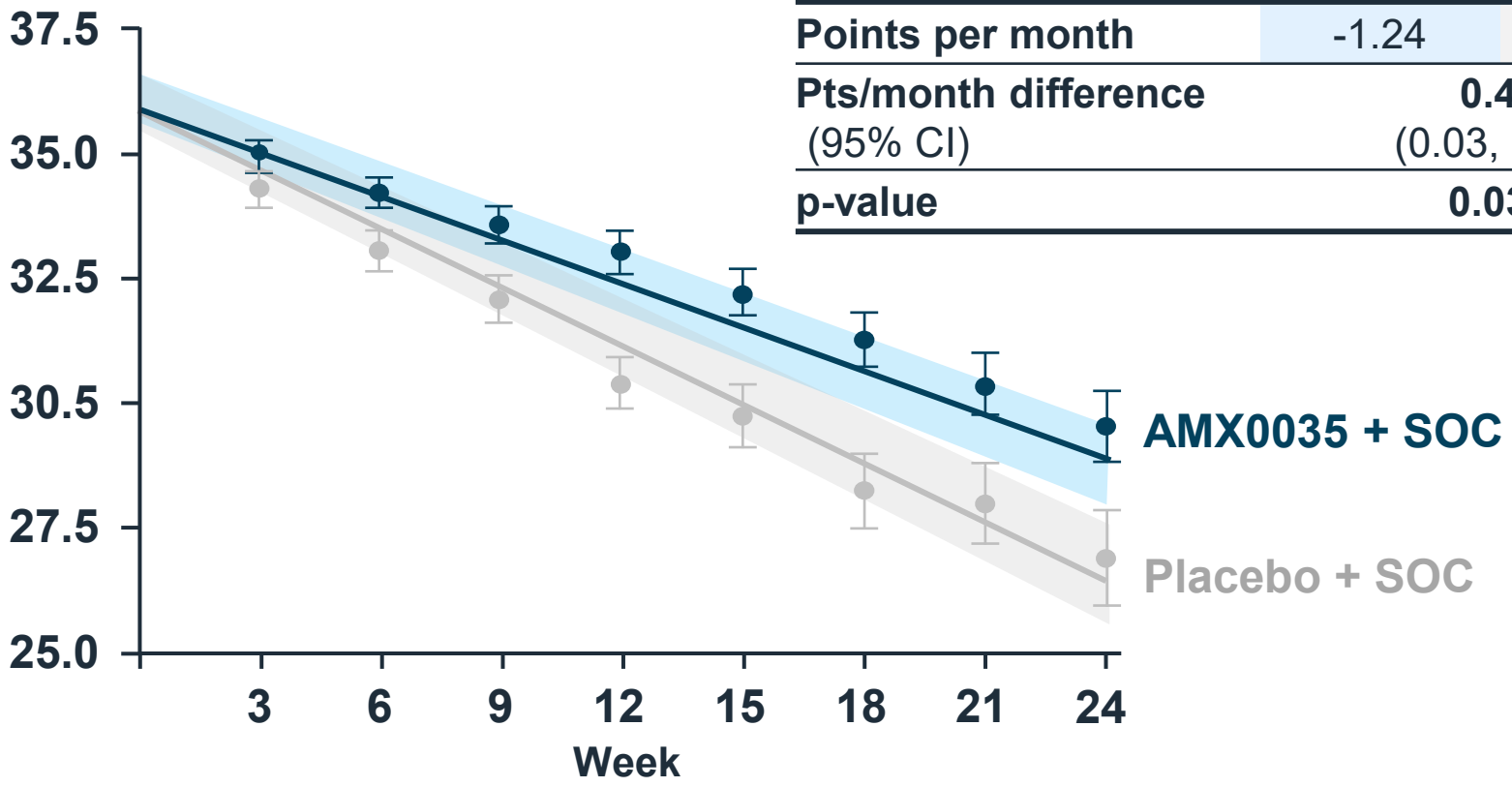
- Shared baseline, linear, mixed effects model with repeated measures
  - Missing at random assumption for missing values
- Model assumes all participants had same baseline ALSFRS-R total score and assumes linearity
- Prespecified quadratic model used instead of linear model if quadratic terms for time in mixed model found significant ($p < 0.10$)
  - All quadratic terms for time per prespecified SAP not significant ($p > 0.10$)
  - Per SAP, only linear terms retained

Joint Rank Analysis Not Appropriate as Primary Endpoint for CENTAUR

Primary Model: Shared baseline, linear, mixed effects model of ALSFRS-R	Joint Rank Analysis of ALSFRS-R
▪ Sensitive estimate of treatment effect	▪ Not sensitive measure of treatment effect due to limited number of deaths in RCP
▪ Able to handle missing data not due to death	▪ No agreed upon method to handle missing data not due to death
▪ Allows inclusion of important prognostic covariates	▪ Cannot adjust for covariates
▪ Clinically meaningful	▪ Provides p-value, but abstract rank statistic not able to translate into clinically meaningful measure by clinicians or people with ALS

RCP Weeks 0-24: AMX0035 Met Primary Endpoint 25% Slower Decline in Function

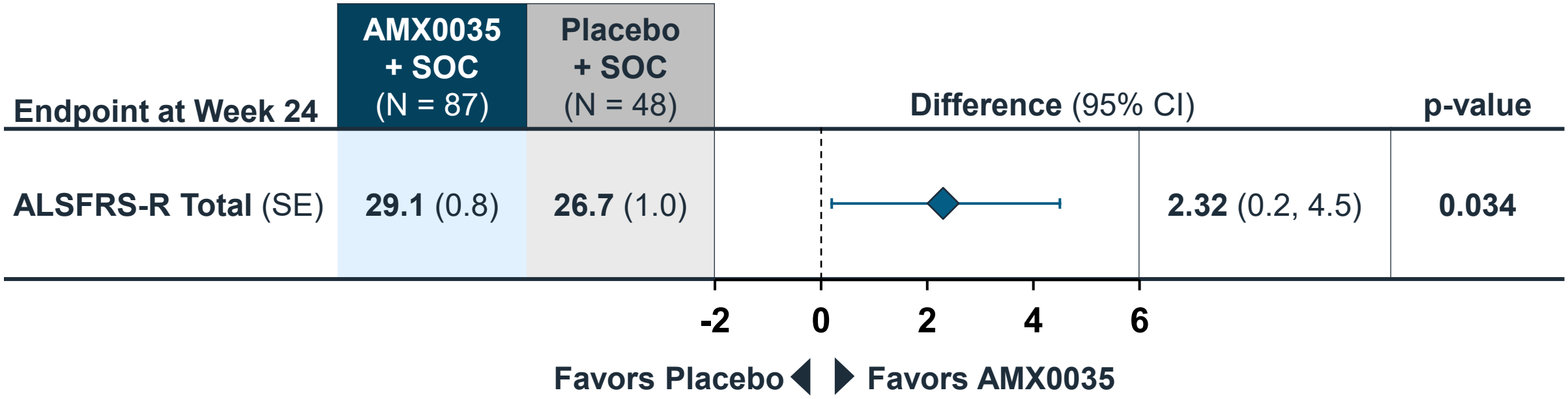
	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Points per month	-1.24	-1.66
Pts/month difference (95% CI)	0.42 (0.03, 0.81)	
p-value	0.034	



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 in mITT Population



mITT Population

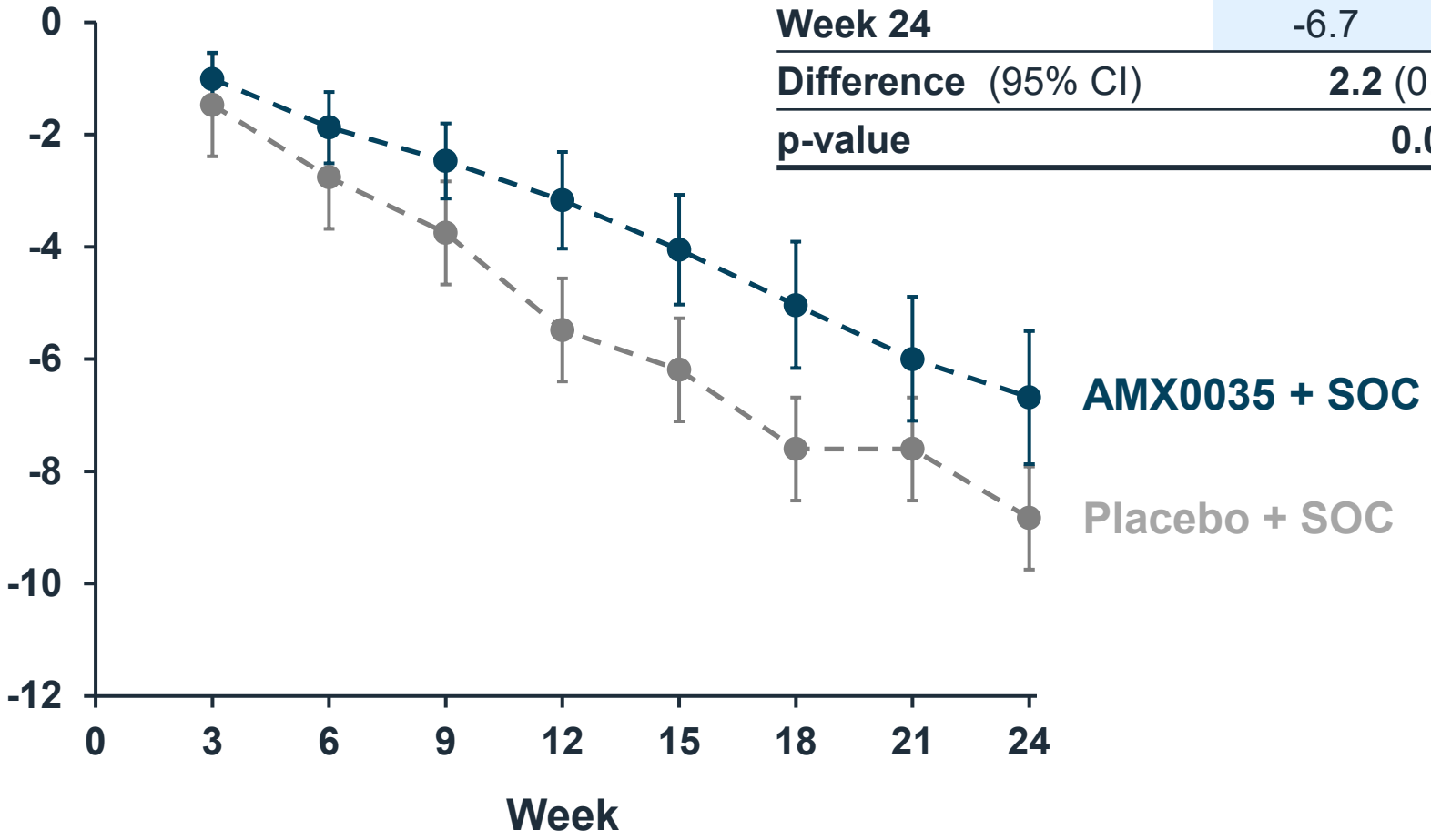
Results Consistent Without Shared Baseline and Linearity Assumptions

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)	Difference (95% CI)	p-value
ALSFRS-R: Linear change from baseline model	**-6.7** (0.7)	**-9.6** (0.9)	**2.9** (0.7, 5.2)	**0.010**
ALSFRS-R: Separate means by visit change from baseline model (traditional MMRM)	**-6.7** (0.6)	**-8.8** (0.8)	**2.2** (0.2, 4.1)	**0.034**

mITT Population

RCP Weeks 0-24: ALSFRS-R Change from Baseline Without Linear Assumption

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Week 24	-6.7	-8.8
Difference (95% CI)	**2.2** (0.2, 4.1)	
p-value	**0.034**	



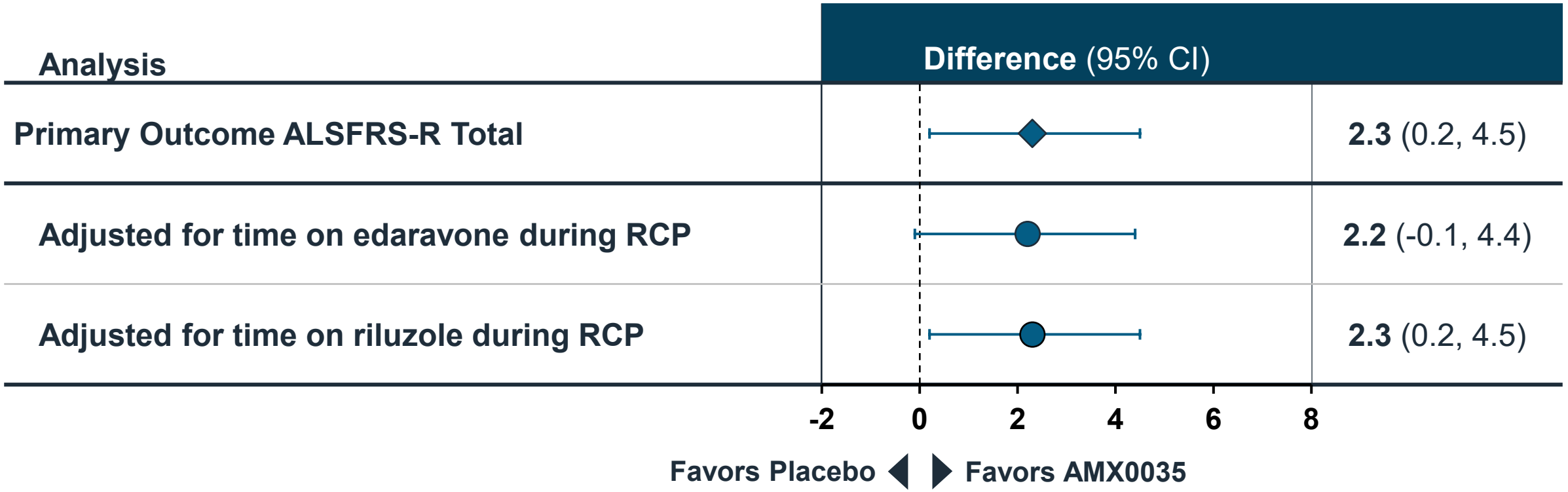
mITT Population

ALSFRS-R Results Similar After Excluding Participants Impacted By Randomization Error

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)

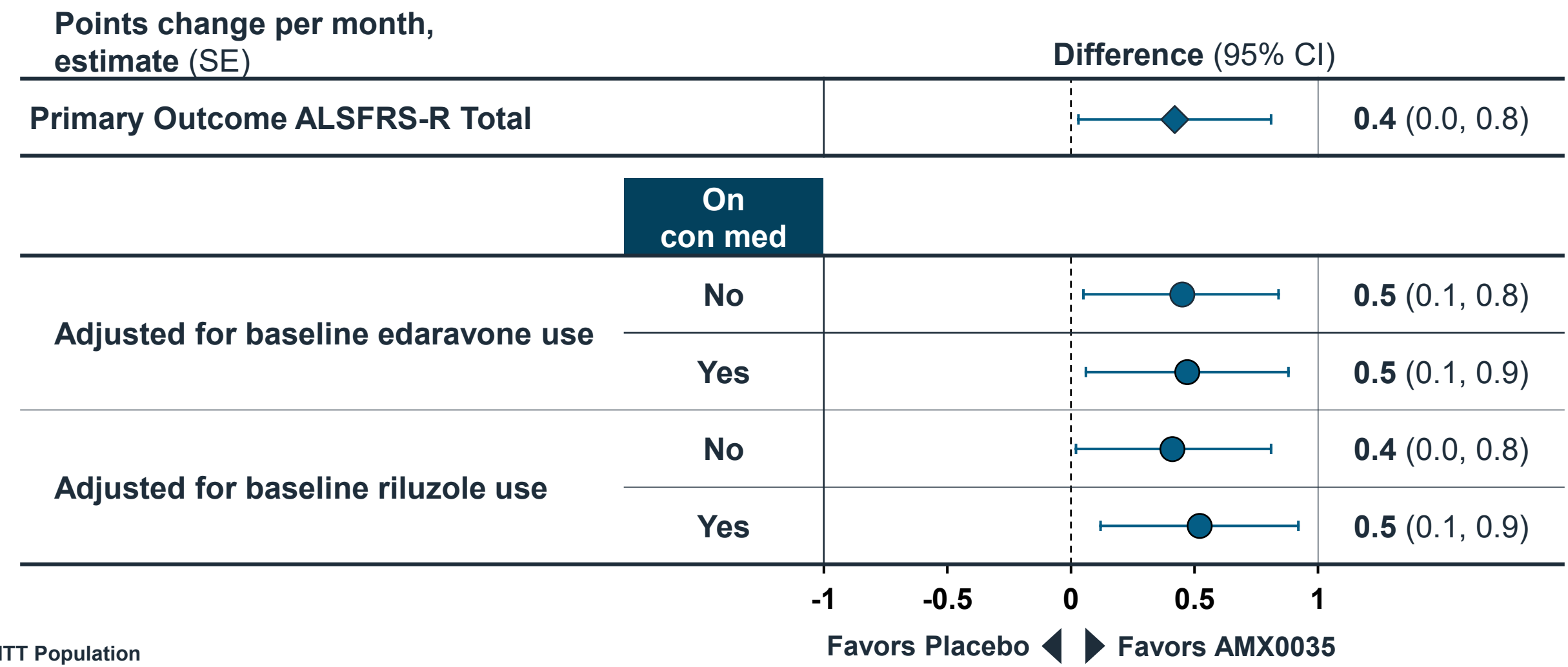
mITT Population

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



mITT Population

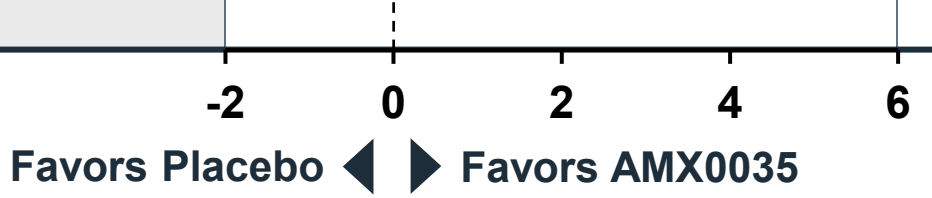
RCP Weeks 0-24: Function Benefit Maintained With or Without Baseline Edaravone and Riluzole Use



mITT Population

RCP Weeks 0-24: Minimal Impact of Missing Data on Primary Endpoint

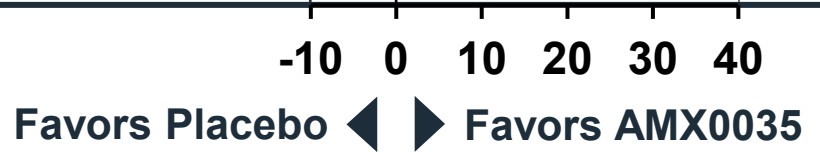
Analysis, estimate (SE)	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)	Difference (95% CI)
Primary Outcome ALSFRS-R Total	**29.1** (0.8)	**26.7** (1.0)	**2.3** (0.2, 4.5)
Multiple imputation for missing data (placebo-based)	**29.7** (0.6)	**27.8** (0.8)	**1.9** (0.1, 3.7)



mITT Population

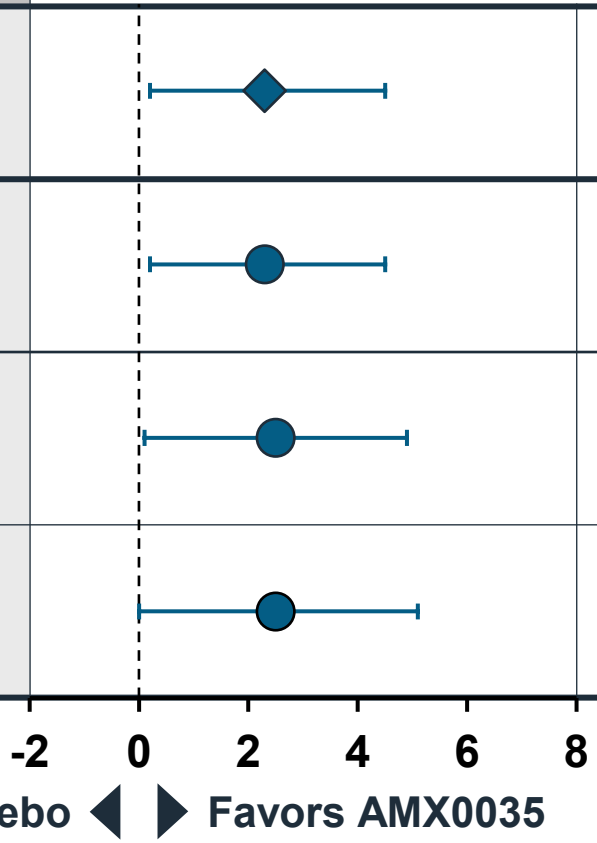
RCP Weeks 0-24: Joint Rank Analyses Accounting for Death Consistent

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**



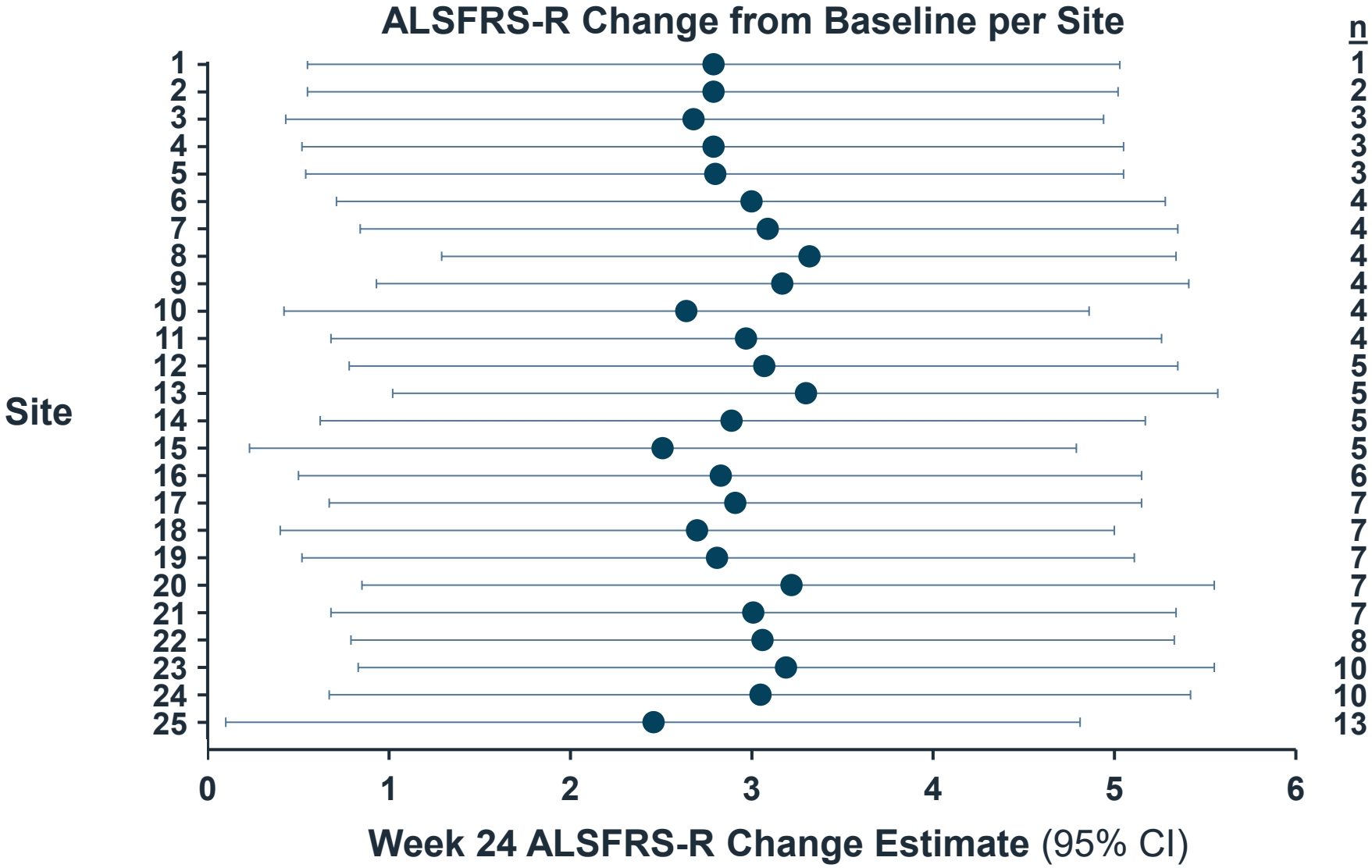
RCP Weeks 0-24: Worst-Case Imputation Accounting for Death on ALSFRS-R Remains Consistent

Analysis, estimate (SE)	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)	Difference (95% CI)	p-value
Primary Outcome ALSFRS-R Total	**29.1** (0.8)	**26.7** (1.0)	**2.3** (0.2, 4.5)	**0.034**
Left-Censored	**29.0** (0.8)	**26.7** (1.0)	**2.3** (0.2, 4.5)	**0.034**
Worst-Case = 7	**28.7** (0.8)	**26.2** (1.1)	**2.5** (0.1, 4.9)	**0.042**
Worst-Case = 0	**28.5** (0.9)	**26.0** (1.1)	**2.5** (0.0, 5.1)	**0.054**



mITT Population

RCP Weeks 0-24: Sensitivity Analysis Showed No Significant Contribution from Any Site



RCP Weeks 0-24: Significant Benefit for AMX0035 in Responder Analysis

Participants, n (%)	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)	Odds Ratio (95% CI)	p-value
Responder	36 **(41%)**	9 **(19%)**	**3.1** (1.3, 7.1)	**0.008**
Non-responder	51 **(59%)**	39 **(81%)**		

mITT Population

Weeks 0-48: Statistically Significant Benefit on Function with AMX0035 Earlier Treatment

Endpoint at Week 48	AMX0035 + SOC* (N = 87)	Placebo + SOC* (N = 48)	Difference (95% CI)	p-value
ALSFRS-R Extended Slope (SE)	**21.6** (1.2)	**17.4** (1.5)	**4.2** (0.6, 7.9)	**0.024**

*Based on original randomized treatment assignment
mITT Population

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

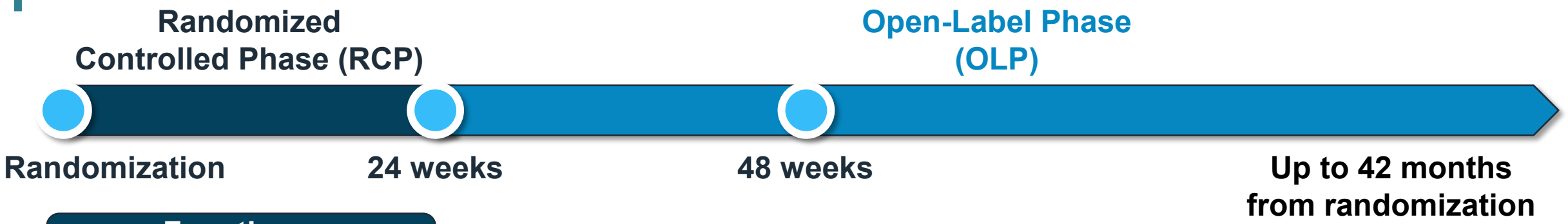
ALSFRS-R slope, Change in points/month	RCP Weeks 0-24	OLP Weeks 24-48**
AMX0035 + SOC*	**-1.24** (n = 87)	**-1.26** (n = 54)
Placebo + SOC*	**-1.66** (n = 48)	**-1.37** (n = 32)

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

Primary Endpoint Met and Robust Across Multiple Sensitivity Analyses

- Statistically significant reduction in rate of progression on ALSFRS-R at end of randomized controlled phase
- Robust across multiple sensitivity analyses
  - Including analyses accounting for missing data due to death
- Sustained benefit of treatment on ALSFRS-R for participants originally randomized to AMX0035 out to Week 48

CENTAUR: Secondary Endpoints Support Function Benefit for AMX0035



Function – Primary Endpoint

Function – Extended Analysis

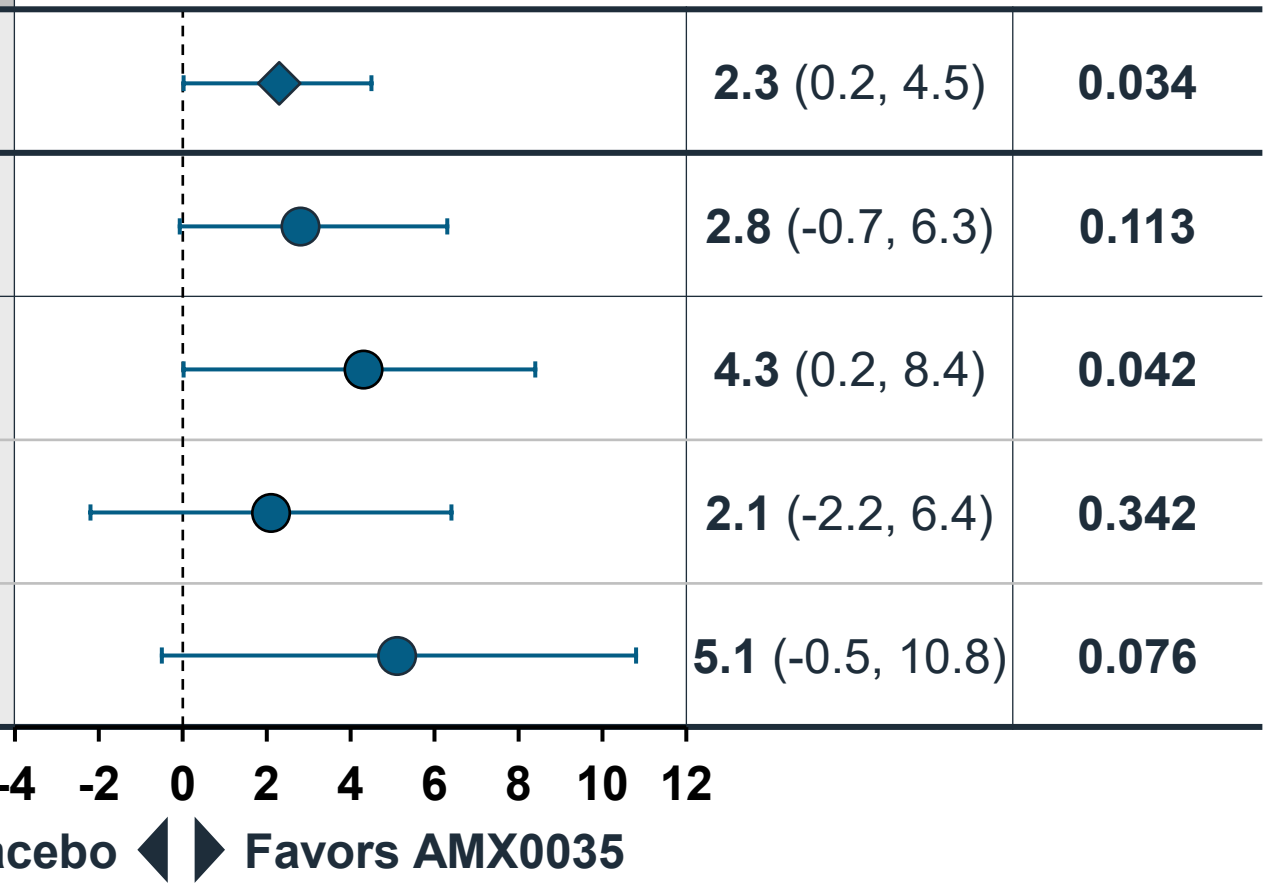
Key Secondary Endpoints

Key Secondary Endpoints – Extended Analysis

Overall survival, time to hospitalization, or death equivalent

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

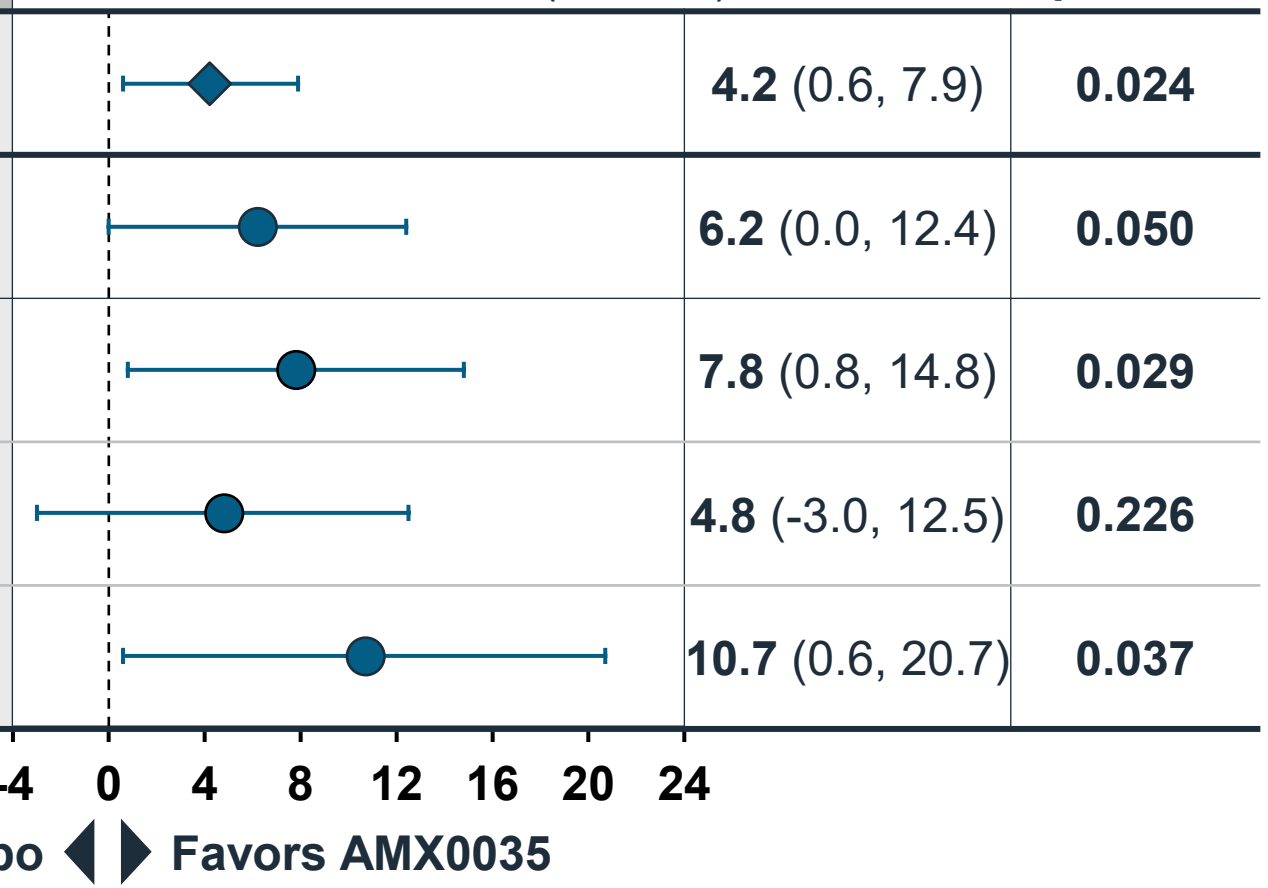
Endpoint	AMX0035 + SOC N	AMX0035 + SOC Estimate (SE)	Placebo + SOC N	Placebo + SOC Estimate (SE)	Difference (95% CI)	p-value
ALSFRS-R Total	87	**29.1** (0.8)	48	**26.7** (1.0)	**2.3** (0.2, 4.5)	**0.034**
Total ATLIS	84	**39.1** (2.0)	47	**36.3** (2.2)	**2.8** (-0.7, 6.3)	**0.113**
Upper limb	85	**36.6** (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

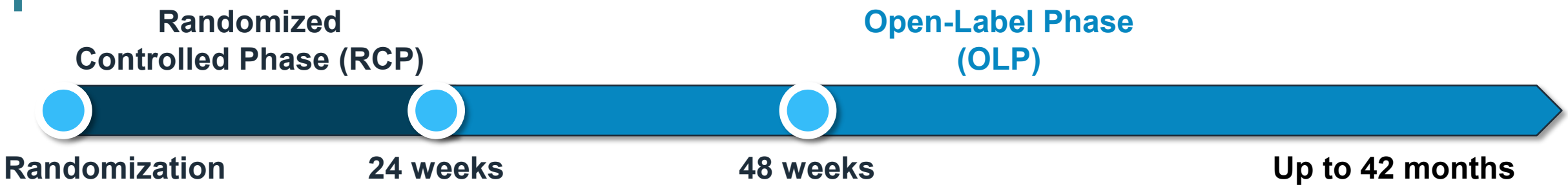
Weeks 0-48: Secondary Endpoints Support Primary Endpoint Results

Endpoint	AMX0035 + SOC N	AMX0035 + SOC Estimate (SE)	Placebo + SOC N	Placebo + SOC Estimate (SE)	Difference (95% CI)	p-value
ALSFRS-R Total	87	**21.6** (1.2)	48	**17.4** (1.5)	**4.2** (0.6, 7.9)	**0.024**
Total ATLIS	84	**22.8** (2.4)	47	**16.7** (3.0)	**6.2** (0.0, 12.4)	**0.050**
Upper limb	85	**19.8** (2.6)	47	**12.1** (3.3)	**7.8** (0.8, 14.8)	**0.029**
Lower limb	85	**25.2** (2.9)	48	**20.5** (3.7)	**4.8** (-3.0, 12.5)	**0.226**
Slow Vital Capacity	87	**48.5** (3.4)	48	**37.9** (4.4)	**10.7** (0.6, 20.7)	**0.037**



*Based on original randomized treatment assignment
mITT Population

CENTAUR: Overall Survival



Function – Primary Endpoint

Function – Extended Analysis

Key Secondary Endpoints

Key Secondary Endpoints – Extended Analysis

Overall survival, time to hospitalization, or death equivalent

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

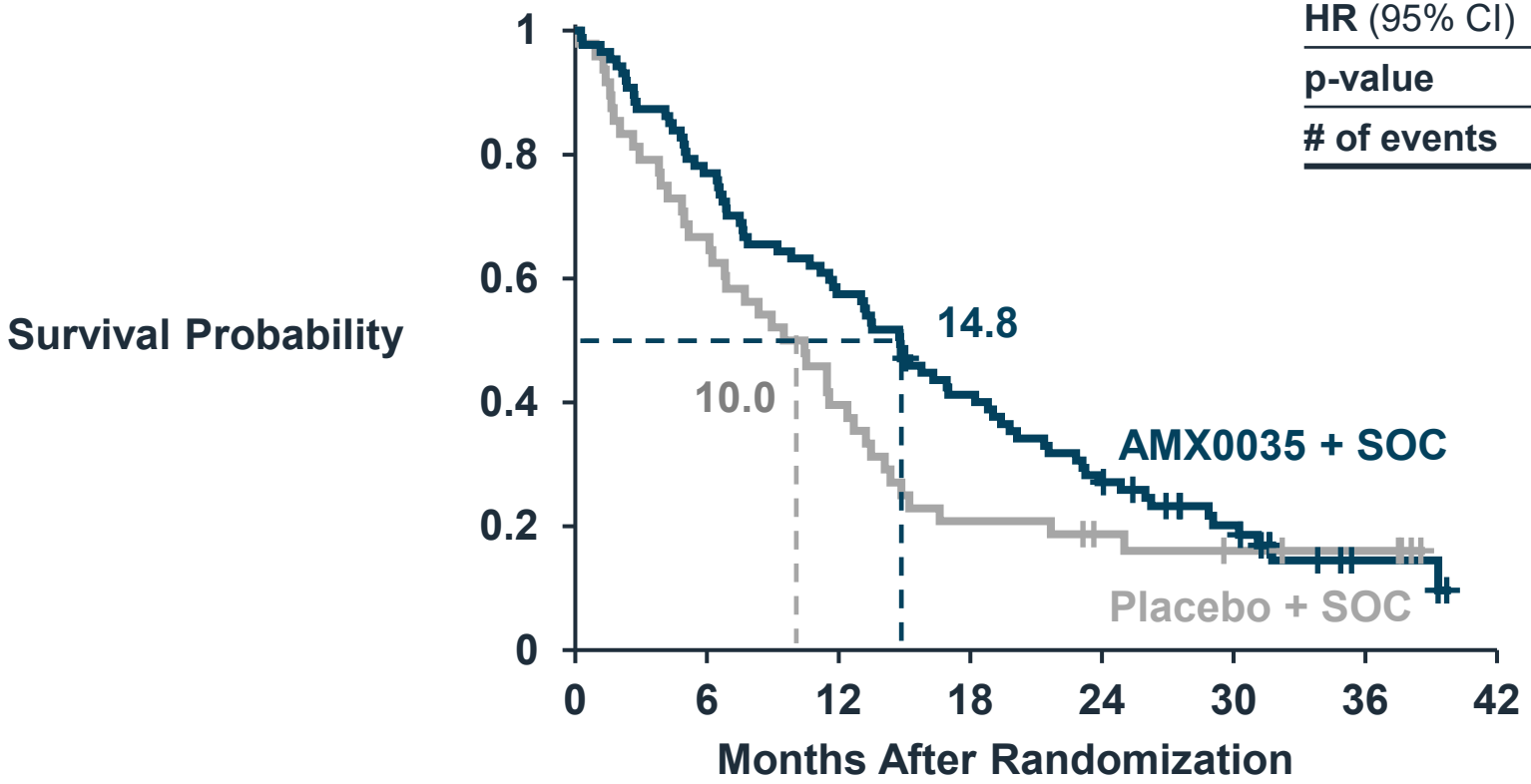
Prespecified Hierarchy for Randomized Controlled Phase	Prespecified Hierarchy for Long-Term Follow-Up
ALSFRS-R rate of decline	ALSFRS-R rate of decline
ATLIS rate of decline	**Impact of AMX0035 on survival, hospitalization, and tracheostomies**
pNF-H rate of decline	Upper and Lower ATLIS scores rate 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	

Time-to-Event Outcomes

- Cut-off: March 2021 (last participant last visit in OLP)
- Comparison groups: originally randomized to AMX0035 + SOC vs placebo + SOC
- Overall Survival (time to death)
  - Comprehensive data capture – 136/137 participants
- Hospitalizations and death equivalent
  - Captured via clinic reports
- Data shown address FDA comments and align with prespecified SAP

Prespecified mITT Overall Survival, Hospitalization, or Death Equivalent Met

	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

mITT Population

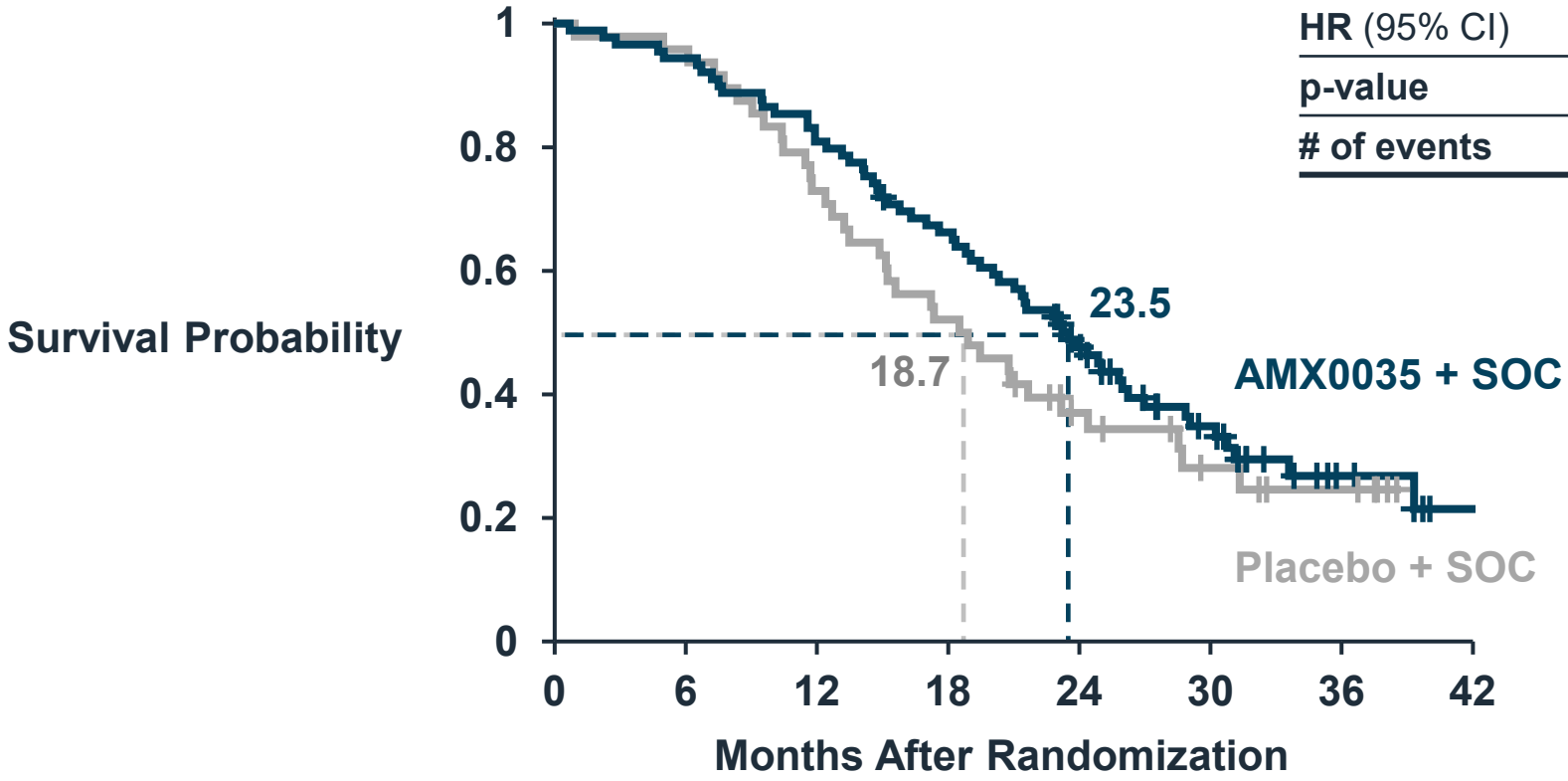
Individual mITT Time to Event Outcomes Show Consistent Benefit for AMX0035

Outcome, median survival estimate	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)	Hazard Ratio (95% CI)
Time to first hospitalization, death, or death equivalent	14.8	10.0	**0.62** (0.42, 0.93)
Time to first hospitalization*	31.8	14.1	**0.62** (0.38, 1.03)
Time to death (overall survival)	23.5	18.7	**0.61** (0.39, 0.95)
Time to death or death equivalent	23.5	17.9	**0.59** (0.38, 0.91)

*Hospitalization defined as at least 24 hour stay
mITT Population

AMX0035 Results in ITT Overall Survival Benefit

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

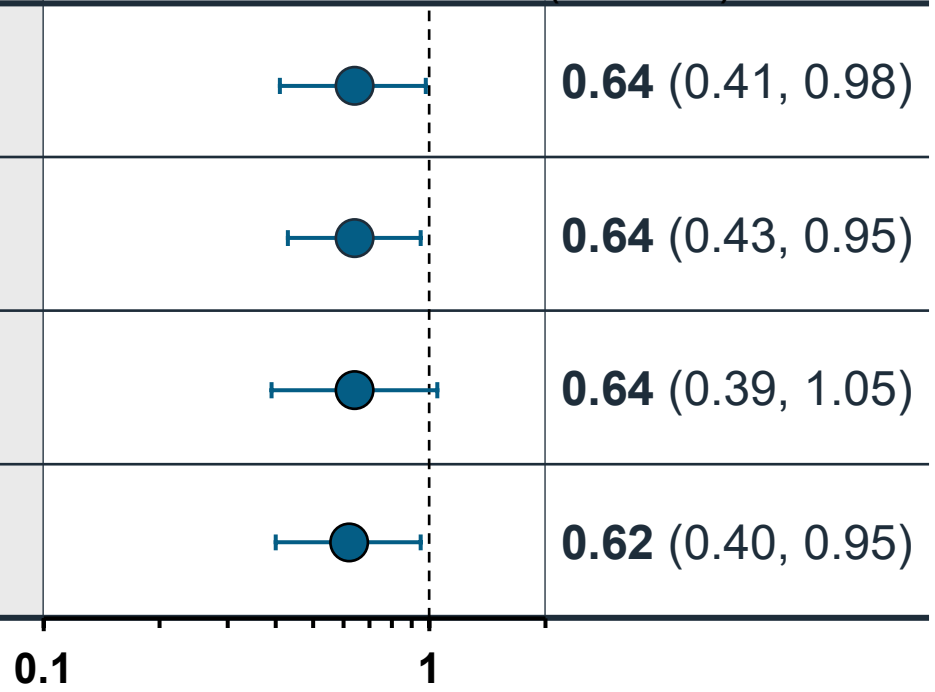


No. at Risk								
Originally Randomized to:	AMX0035 + SOC	89	84	72	58	38	21	6	1
	Placebo + SOC	48	46	35	25	14	8	5	0

ITT Population

Composite and Individual Time to Event Benefit Consistent in ITT Population

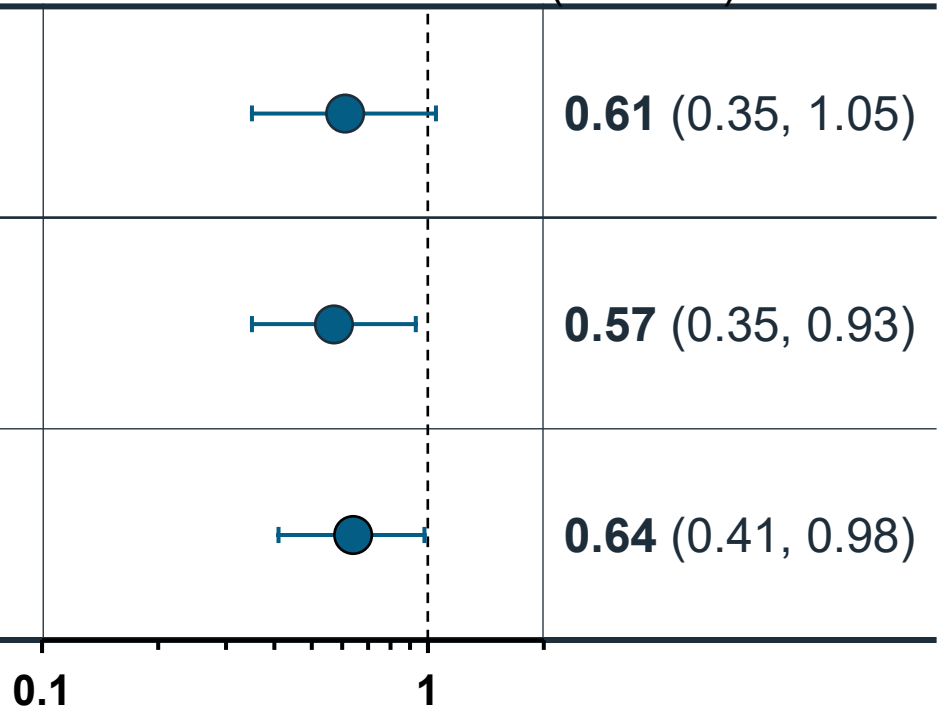
Outcome, median survival estimate	AMX0035 + SOC (N = 89)	Placebo + SOC (N = 48)	Hazard Ratio (95% CI)
Time to death (overall survival)	23.5	18.7	**0.64** (0.41, 0.98)
Time to first hospitalization, death, or death equivalent	14.8	10.0	**0.64** (0.43, 0.95)
Time to first hospitalization	31.8	14.1	**0.64** (0.39, 1.05)
Time to death or death equivalent	23.2	17.9	**0.62** (0.40, 0.95)



ITT Population

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)



ITT Population

Addressing FDA Comments

FDA Concern	Response
Taste, GI AEs, blinding throughout OLP	▪ GI AEs and study drug taste unlikely to lead to unblinding
Choice of primary analysis	▪ Use of linear terms supported by prespecified sensitivity analyses ▪ Joint rank not appropriate and less sensitive primary outcome ▪ Performed as sensitivity analysis, and results consistent with prespecified primary analysis
Survival methodology	▪ Ensured alignment of data presented with pre-specified statistical analysis plan ▪ Regardless of cut-off date, survival benefit for AMX0035 consistent
Statistical differences	▪ Performed additional analyses to investigate assumptions leading to FDA results and all support robustness of data

AMX0035 Gives People Living with ALS More Valuable Time

- Statistically significant and clinically meaningful benefit on both function and survival
- Prespecified primary outcome met and robust across multiple sensitivity analyses and on top of standard of care
- Clinical secondary outcomes measuring clinical decline consistent with primary outcome
- Long-term prespecified time to event outcome met
- ITT overall survival benefit in universally fatal disease

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

Totality of 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

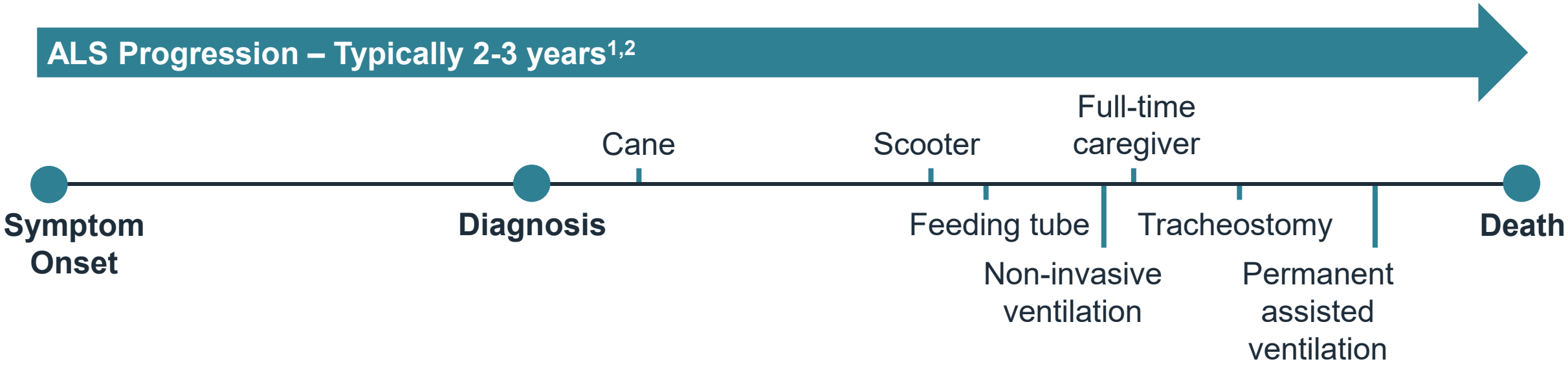
- GI events, generally mild and transient

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

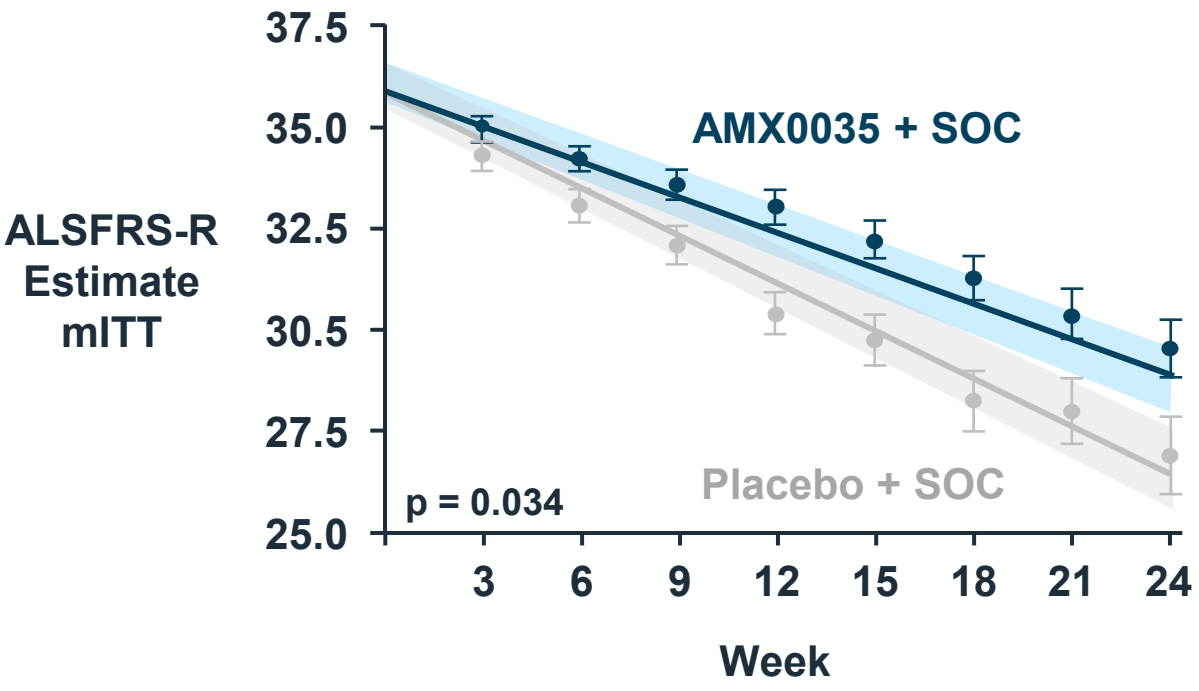


Two currently approved treatments for ALS show either benefit for survival or slowing in functional decline[3,4,5]
Neither has demonstrated both in trials that led to their approval[3,4,5]

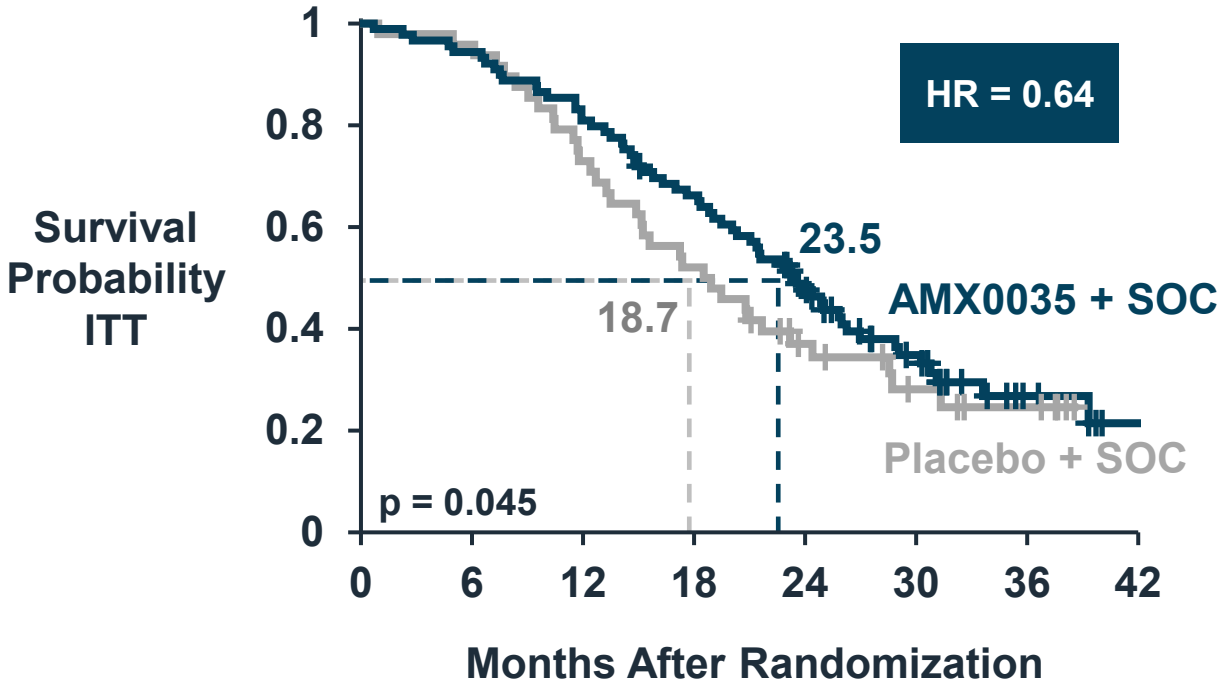
1.Paganoni, 2014; 2.Chiò, 2009; 3. Riluzole FDA Label; 4.Edaravone FDA Label; 5. Writing Group, 2017

AMX0035 Combines Benefits to Both Function and Survival

25% Slower Decline in Function



4.8 Months Longer Median Survival



Additional measures of muscle strength, respiratory function, and time to key events support functional and survival outcomes

AMX0035 Favorable Clinical Profile

- Easy to administer by mouth or feeding tube
- Well-tolerated
- Gastrointestinal side effects of nausea, diarrhea, and abdominal pain generally mild or moderate and manageable
- Can be administered with riluzole and/or edaravone

Evidence Supports Use of AMX0035

- Important to look at results in context of rare, fatal disease
- Phase 3 trial underway represents commitment to ALS community
- CENTAUR study met prespecified primary outcome
  - Clinically meaningful benefit on function and survival
  - Favorable safety profile
  - Outcomes that matter to patients

AMX0035

March 30, 2022

Amylyx Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee