AMX0035

September 07, 2022

Amylyx Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee
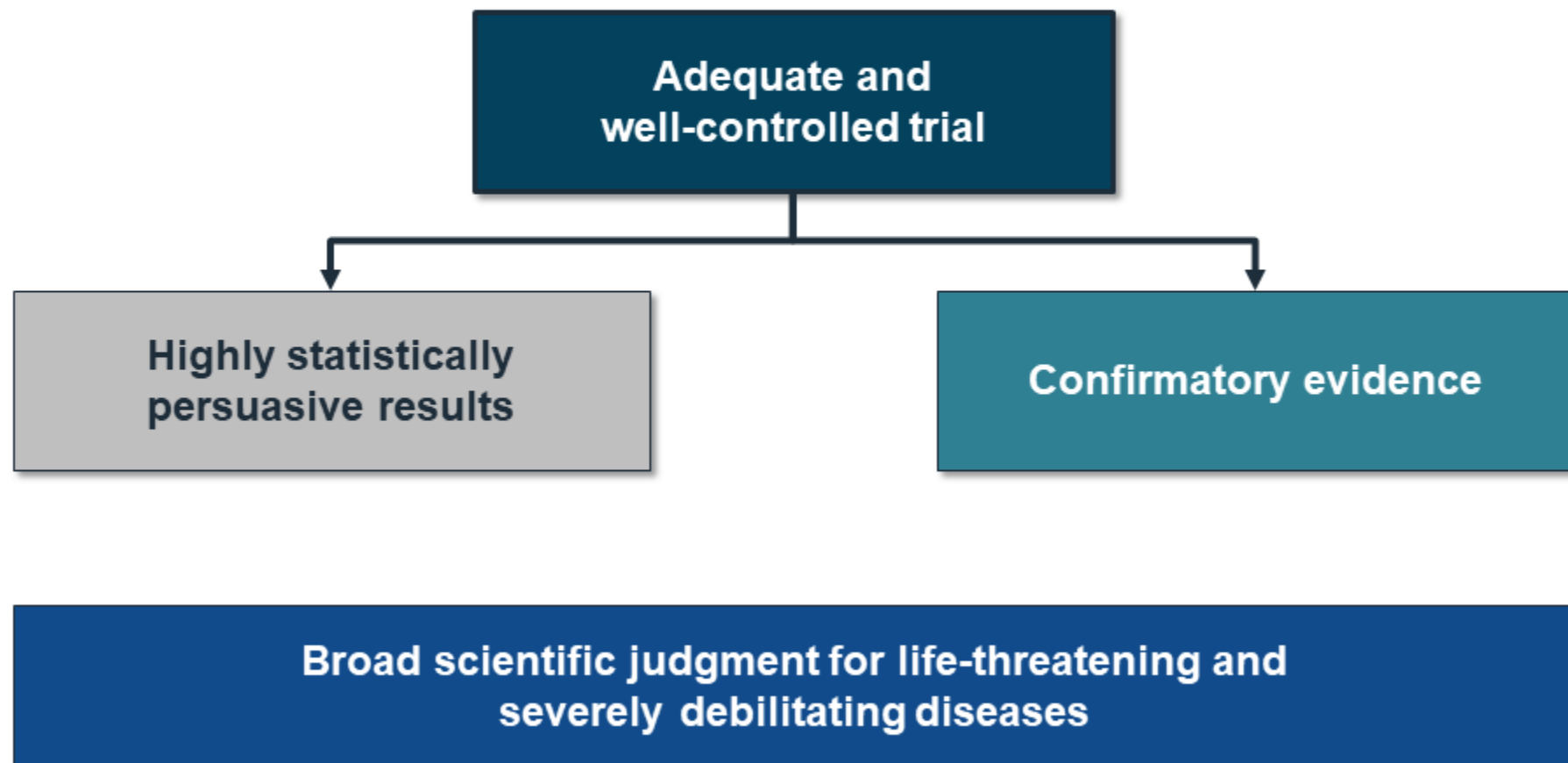
Introduction

Tammy Sarnelli

Global Head of Regulatory Affairs

Amylyx Pharmaceuticals

AMX0035 Met Primary Endpoint and Showed Robust Survival Benefit

Primary Analysis of Effectiveness	Difference	p-value
ALSFRS-R	2.3 points	0.034
Survival Benefit		
ITT OS	4.8 months	0.045

ALSFRS-R = ALS Functional Rating Scale – Revised; ITT OS = Intent to Treat Population Overall Survival

Two Options for Meeting Substantial Evidence of Efficacy Based on Single Trial

Adequate and well-controlled trial

Highly statistically persuasive results

Confirmatory evidence

Broad scientific judgment for life-threatening and severely debilitating diseases

ITT Overall Survival Is Confirmatory Evidence

Adequate and Well-controlled Trial	**CENTAUR** Met prespecified primary endpoint
Confirmatory Evidence	ITT Overall Survival

- **2017 FDA Guidance:** *"For many serious diseases, there is an endpoint of such great clinical importance that it is unreasonable not to collect and analyze the endpoint data; the usual example is **mortality**..."*

FDA Draft Guidance *Multiple Endpoints in Clinical Trials*, January 2017

FDA Guidance Allows for Use of Concurrent or External Controls to Confirm Benefit

- ITT Overall Survival used conservative analysis
- 2019 Substantial Evidence Guidance
  - Survival may be ascertained using either concurrent or external controls
  - May be further confirmed by data from separate sources such as natural history as confirmatory evidence

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, December 2019

Three New Analyses Confirm ITT OS Benefit

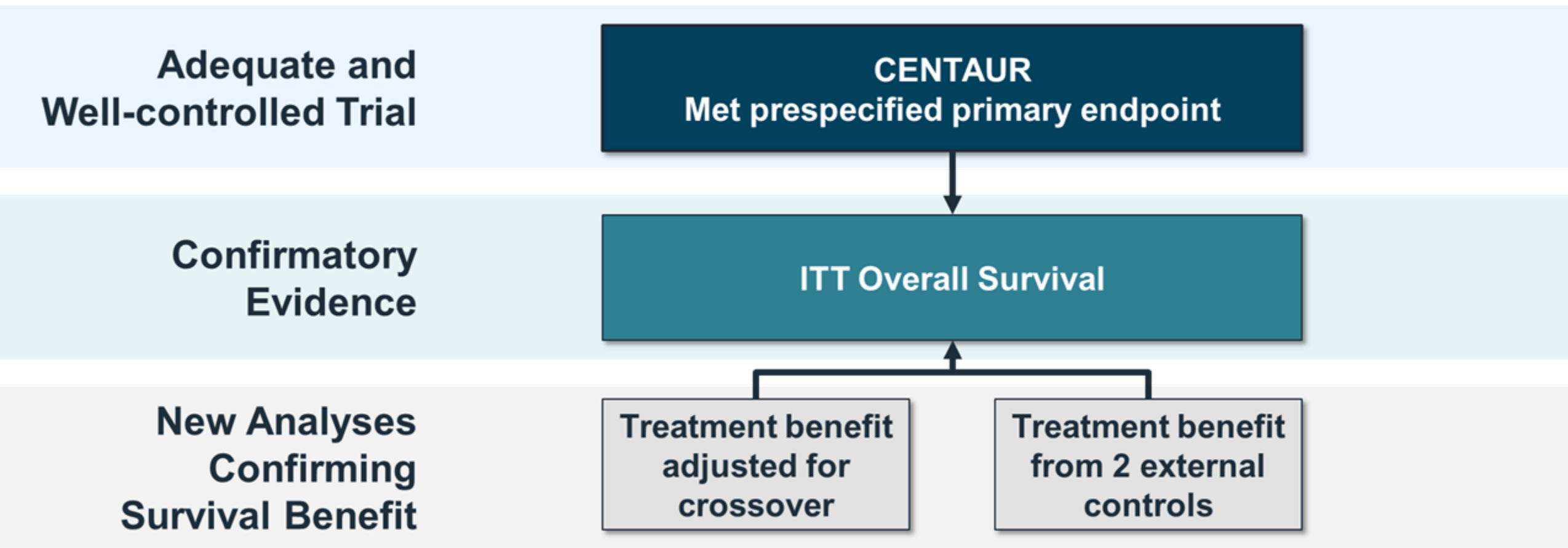|	
Adequate and Well-controlled Trial	**CENTAUR** Met prespecified primary endpoint
Confirmatory Evidence	**ITT Overall Survival**
New Analyses Confirming Survival Benefit	Treatment benefit adjusted for crossover / Treatment benefit from 2 external controls

AMX0035 Meets Regulatory Standard for Single Study with Confirmatory Evidence

Primary Analysis of Effectiveness	Difference	p-value
ALSFRS-R	2.3 points	0.034
Confirmatory Survival Benefit		
ITT OS	4.8 months	0.045
New Survival Analyses with Different Control Groups		
Crossover-adjusted placebo arm comparison	9.7 months	0.045
Natural history survival prediction external control arm comparison	9.9 months	< 0.0001
Propensity score matched historical clinical trial external control arm comparison	11.0 months	0.0002

Key Regulatory Milestones

PHOENIX Timeline

FDA Review→

2021	2022	2023	2024	2025
Start of PHOENIX trial	FDA review of AMX0035		PHOENIX complete	AMX0035 potential availability if not approved in 2022

- FDA advised Amylyx to submit NDA based on CENTAUR alone and before start of PHOENIX

- Currently > 350 participants enrolled in Phase 3 PHOENIX study across ~65 sites

- Approved in Canada with condition to complete PHOENIX

Agenda

Current Landscape in ALS

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

Biomarker Data

Lahar Mehta, MD
Head of Global Clinical Development
Amylyx Pharmaceuticals

CENTAUR Results and New Overall Survival Analyses

Jamie Timmons, MD
Head of Scientific Communications
Amylyx Pharmaceuticals

Clinical Perspective

Merit E. Cudkowicz, MD, MSc
Chief, Neurology Department and Director,
Sean M. Healey and AMG Center for ALS
Massachusetts General Hospital
Julieanne Dorn Professor of Neurology,
Harvard Medical School

Additional Experts

James Berry, MD, PhD
First to publish on joint-rank methods in ALS
Director, MGH Neurological Clinical Research Institute (NCRI)

Robert Bowser, PhD
ALS biomarker expert
Chief Scientific Officer
Professor, Barrow Neurological Institute

Suzanne Hendrix, PhD
Conducted primary analysis of CENTAUR
Biostatistician, CEO
Pentara Corporation

Melanie Quintana, PhD
Director & Senior Statistical Scientist
Berry Consultants, LLC

James Robins, MD
Co-inventor RPSFTM
Mitchell L. and Robin LaFoley Dong Professor of Epidemiology
Harvard T.H. Chan School of Public Health

David Schoenfeld, PhD
Co-inventor of Finkelstein-Schoenfeld (joint-rank) method
Biostatistics Center, Massachusetts General Hospital
Professor Emeritus, Harvard Medical School

Jeremy Shefner, MD, PhD
Leading expert in ALS clinical trials, CENTAUR outcomes training
Senior Vice President
Kemper and Ethel Marley Professor and Chair of Neurology
Barrow Neurological Institute

Current Landscape in ALS

Sabrina Paganoni, MD, PhD

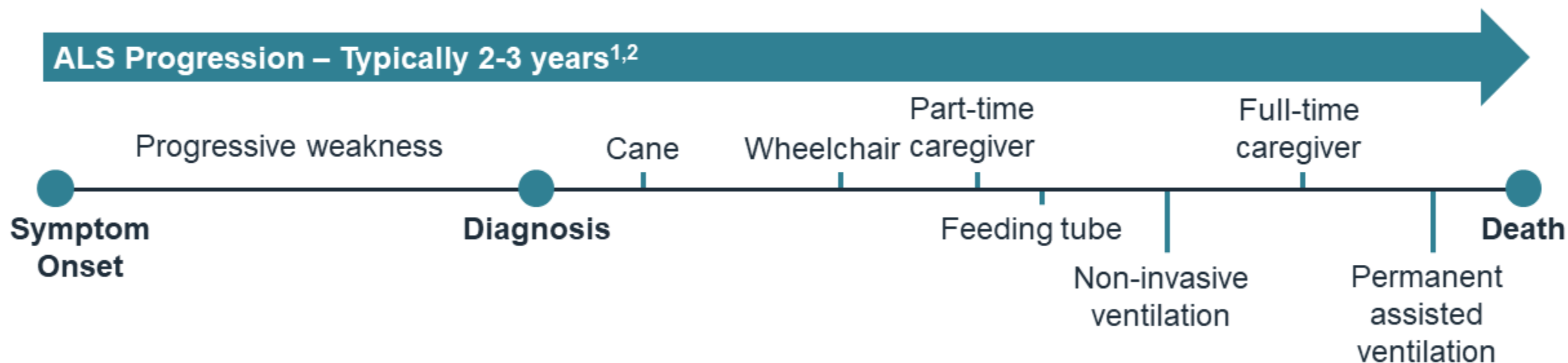Co-Director, Neurological Clinical Research Institute

Sean M. Healey & AMG Center for ALS

Massachusetts General Hospital

Associate Professor, Harvard Medical School

ALS – Series of Unrelenting and Irreversible Losses

ALS Progression – Typically 2-3 years[1,2]

Progressive weakness

Part-time
Wheelchair caregiver

Full-time
caregiver

Cane

Symptom Onset

Diagnosis

Feeding tube

Non-invasive
ventilation

Permanent
assisted
ventilation

Death

- Median survival ~ 2 years from diagnosis[3]
    - Time to diagnosis on average 12 months in the US[1]

1. Paganoni, 2014; 2. Chiò, 2009; 3. Karanevich, 2018

Only Two Approved Products for ALS in US

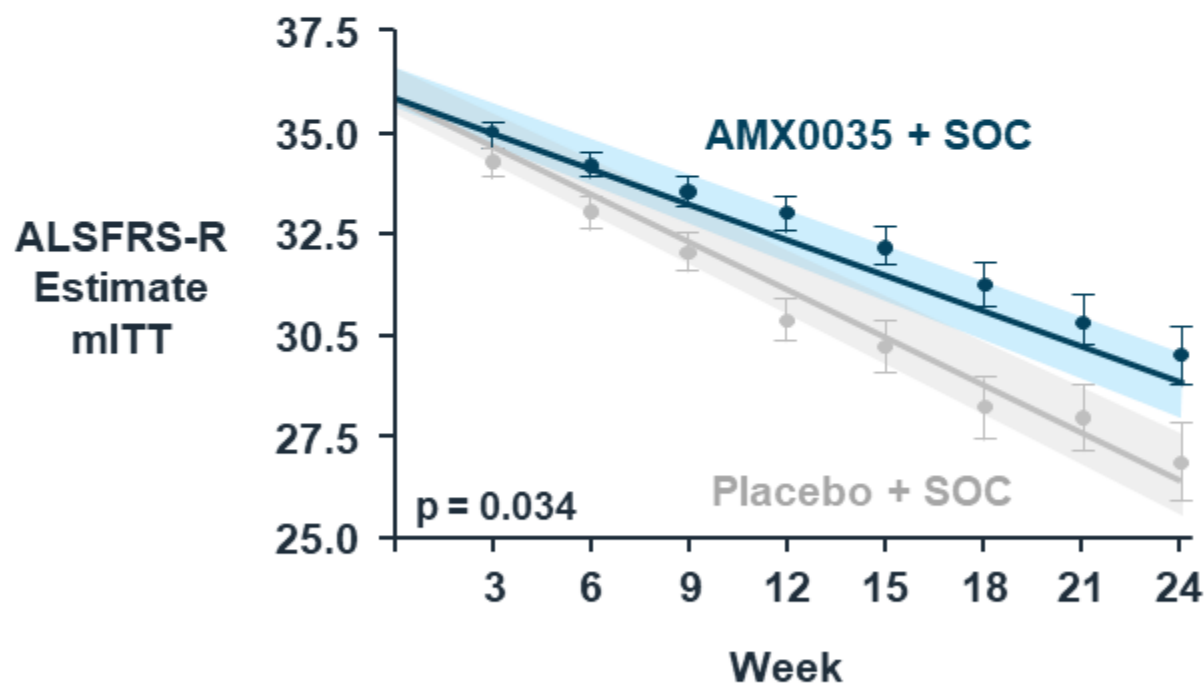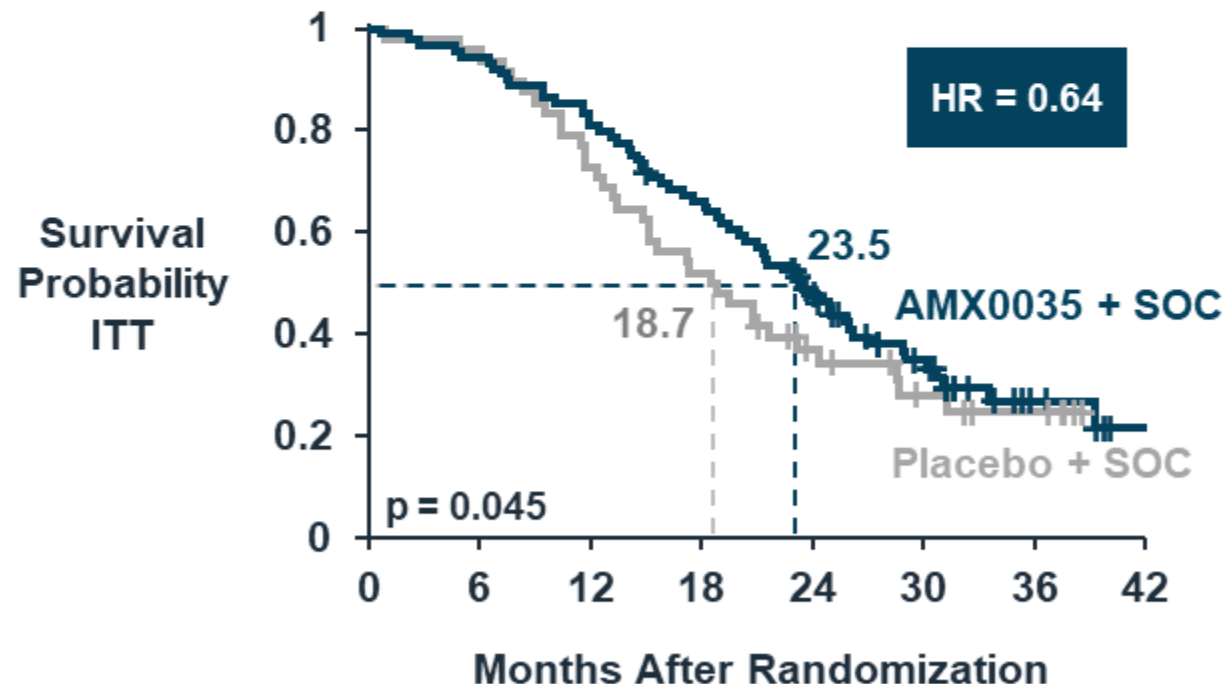| Riluzole (1995)[1]	Edaravone (2017)
▪ 2 to 3-months difference primary outcome median time to death or tracheostomy ▪ Differences in function not observed	▪ Slowed disease progression primary outcome (ALSFRS-R)[2] ▪ Differences not observed on secondary outcomes of strength, vital capacity, or survival[3]

Two currently approved treatments for ALS show either benefit on survival or slowing in functional decline[1,2]
Neither demonstrated both in trials that led to their approval[1-3]

Nuedexta is indicated for the treatment of pseudobulbar affect in ALS[4]
1. Riluzole FDA Label; 2. Edaravone FDA Label; 3. Writing Group, 2017; 4. Nuedexta FDA Label

AMX0035 Showed Significant and Meaningful Impact on Endpoints That Matter

25% Slower Decline in Function

ALSFRS-R Estimate mITT

AMX0035 + SOC

Placebo + SOC

p = 0.034

Week
3 6 9 12 15 18 21 24

37.5
35.0
32.5
30.5
27.5
25.0

4.8 Months Longer Median Survival

Survival Probability ITT

HR = 0.64

23.5

AMX0035 + SOC

18.7

Placebo + SOC

p = 0.045

Months After Randomization
0 6 12 18 24 30 36 42

1
0.8
0.6
0.4
0.2
0

SOC = Standard of Care

CENTAUR – Blueprint for Current ALS Trials Capturing and Analyzing Survival Data

- CENTAUR captured meaningful survival data while limiting time on placebo
  - ITT Overall Survival
- External controls help to further understand impact of AMX0035 on survival
  - Well-characterized, known predictors of survival
  - ENCALS prediction model + PRO-ACT clinical trial database

Biomarkers in Neurodegenerative Diseases: Significant Progress but Still Evolving in ALS

- Interesting developments, still learning

- Biomarkers of interest in ALS

  - Neurofilaments: NfL, pNfH[1,2]

  - Markers of neuroinflammation: CHIT1, CHI3L1 / YKL-40[2,3]

  - Chemokines, cytokines[2]

  - Total tau, p-tau[2]

  - p75[ECD,4]

NfL = neurofilament light; pNfH = phosphorylated neurofilament heavy; CHIT1 = chitotriosidase 1; CHI3L1/ YKL-40 = Chitinase-3-like protein 1;
p-tau = phosphorylated tau; p75[ECD] = urinary neurotrophin receptor p75 extracellular domain
1. Benatar, 2020; 2. Dreger, 2022; 3. Masrori, 2022; 4. Shepheard, 2017

Urgently Need Treatments for ALS

- People living with ALS have short life expectancy and there is no cure

- Symptoms have already started to take over by time of diagnosis

- People living with ALS want to retain function for as long as possible

- Neither currently approved treatments for ALS show <u>both</u> slowing in functional decline and benefit for survival

- AMX0035 ability to help people live longer and have function for longer is what matters

Biomarker Data

Lahar Mehta, MD

Head of Global Clinical Development

Amylyx Pharmaceuticals

Background on Biomarker Assessment in AMX0035 Clinical Studies

CENTAUR

- ALS
- 24-week duration
- 137 participants
- Plasma biomarkers
    - Neurofilaments

PEGASUS

- Alzheimer's disease
- 24-week duration
- 95 participants
- CSF biomarkers
    - Panel of 18 biomarkers

CSF = Cerebrospinal Fluid

PEGASUS – AMX0035 Improves Several CSF Biomarkers in Alzheimer's Disease

CSF Biomarkers	AMX0035	Placebo	Week 24 LS Mean (95% CI) Difference between AMX0035 and Placebo	p-value
YKL-40 (CHI3L1) (ng/mL)	-14.6	1.5	-16.1 (-27.0, -5.3)	0.004
Total Tau (pg/mL)	-64.9	8.8	-73.7 (-106.8, -40.7)	< 0.0001
Phosphorylated Tau (pTau181) (pg/mL)	-14.6	-0.3	-14.4 (-21.5, -7.2)	0.0002
Neurogranin (pg/mL)	-81.2	-8.3	-72.9 (-110.8, -34.9)	0.0003
FABP3 (pg/mL)	-344.6	102.9	-447.5 (-684.6, -210.5)	0.0004
$A\beta_{42}$ / $A\beta_{40}$ Ratio (pg/mL)	0.004	-0.005	0.009 (0.003, 0.02)	0.005

- Not significantly improved: NfL, IL-6, IL-8, GFAP, MCP-1, $A\beta_{42}$, $A\beta_{40}$, 24-OHC, Leptin, sIR, MMP-10

CENTAUR – Lower Levels of YKL-40 in ALS at Week 24 with AMX0035 vs Placebo (Preliminary)

Plasma Biomarker	Week 24 Geometric LS Mean (SE)		Geometric LS Mean Ratio (95% CI)	p-value
	AMX0035	Placebo		
YKL-40 (ng/mL)*	31.4 (1.1)	38.8 (1.1)	0.8 (0.7, 0.9)	0.0078

- Concentration of YKL-40 shown to correlate with ALS severity[1-3], speed of disease progression[4-6], and survival[7]

- In CENTAUR, correlation of YKL-40 to ALSFRS-R score (r = -0.21, p = 0.0001) and ALSFRS-R progression rate (r = -0.19, p = 0.004)

*Data were log-transformed prior to analysis as per Vu, 2020[4]

1. Dreger, 2022; 2. Oeckl, 2018; 3. Thompson, 2019; 4. Vu, 2020; 5. Gille, 2019; 6. Andres-Benito, 2018; 7. Masrori, 2022

CENTAUR Results and New Overall Survival Analyses

Jamie Timmons, MD

Head of Scientific Communications

Amylyx Pharmaceuticals

AMX0035 Meets Regulatory Standard for Substantial Evidence of Effectiveness

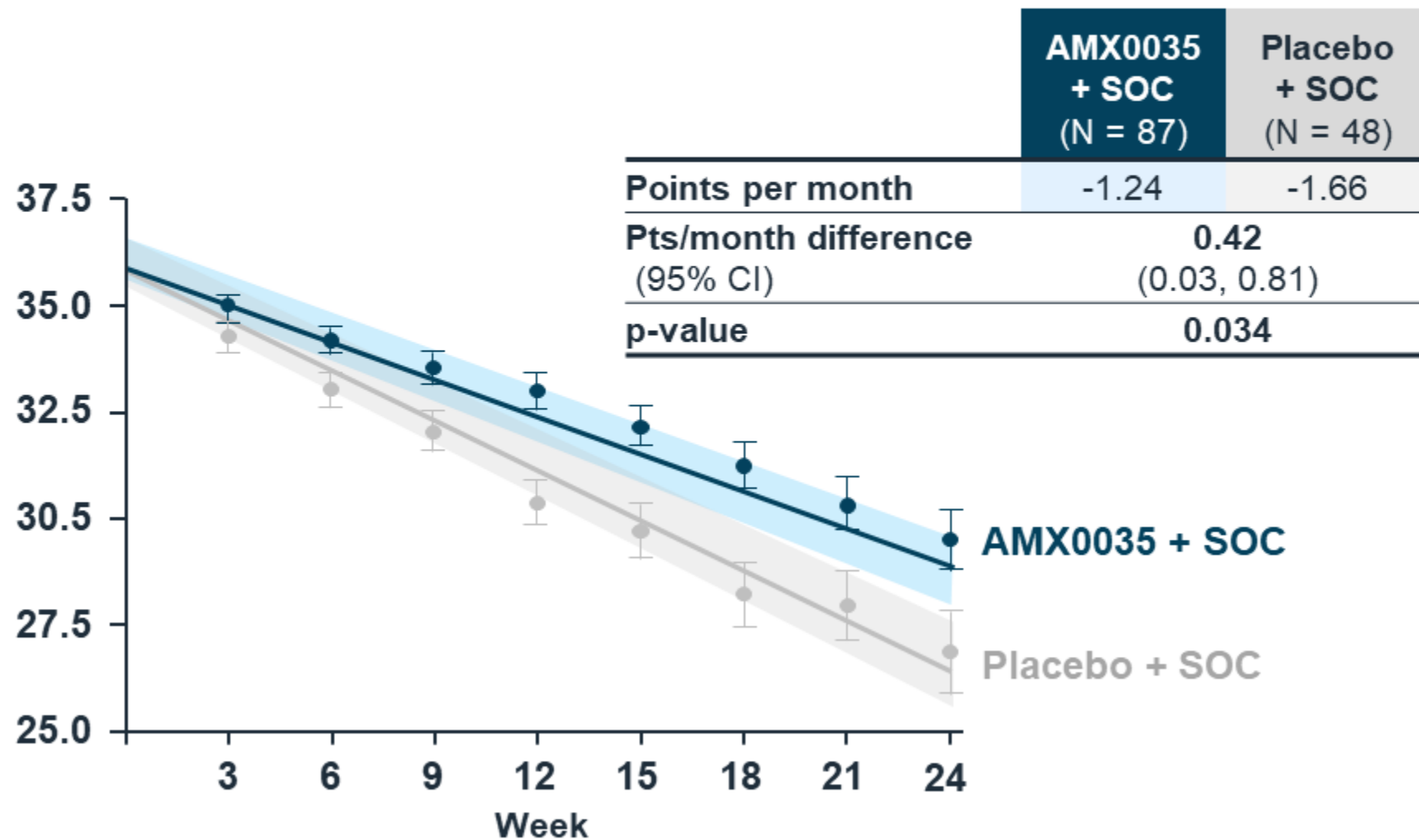| Adequate and Well-controlled Trial	**CENTAUR** Met prespecified primary endpoint
Confirmatory Evidence	**ITT Overall Survival**
New Analyses Confirming Survival Benefit	**Treatment benefit adjusted for crossover** **Treatment benefit from 2 external controls**

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, December 2019

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	

ALSFRS-R Estimate

AMX0035 + SOC

Placebo + SOC

Week

mITT population

CENTAUR – Robust and Positive Trial

- Primary model: shared baseline, linear, mixed effects model
  - Consistent without shared baseline (p = 0.01) and linearity (p = 0.03) assumptions
  - Consistent results when accounting for concomitant use of riluzole and edaravone
    - In-study edaravone starts also did not impact results (p = 0.04)
- Sensitive estimate of treatment effect given few deaths at Week 24
  - 5 (5.6%) on AMX0035; 2 (4.2%) on placebo
- In-study deaths accounted for using sensitivity analyses
  - Each analysis consistent with prespecified result, including joint rank
    - Both Amylyx and FDA joint rank analyses yield (p = 0.05) in prespecified mITT population

AMX0035 Meets Regulatory Standard for Substantial Evidence of Effectiveness

Adequate and Well-controlled Trial	**CENTAUR** **Met prespecified primary endpoint**	
Confirmatory Evidence	**ITT Overall Survival**	
New Analyses Confirming Survival Benefit	Treatment benefit adjusted for crossover	Treatment benefit from 2 external controls

FDA Draft Guidance *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, December 2019

Robustness of ITT Overall Survival Result

- Placebo-controlled analysis with confirmed survival status in 136 / 137 patients

- Survival prognosis well-balanced between groups

- Concomitant medication use did not impact result

- Results consistent across timepoints of analysis

ITT Overall Survival Analysis Was Placebo Controlled

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                    (n = 89)  ┌────────────────────────────────────────────┐
                    ─────────►│       Randomized to AMX0035                 │
                              └────────────────────────────────────────────┘
┌──────────────┐
│ Randomized   │                                                              Up to
│    2:1       │              Investigators and participants blinded          42 months
│  (N = 137)   │              to original treatment throughout study          from
│              │                                                              randomization
└──────────────┘
                    ─────────►┌────────────────────────────────────────────┐
                    (n = 48)  │        Randomized to Placebo                │
                              └────────────────────────────────────────────┘
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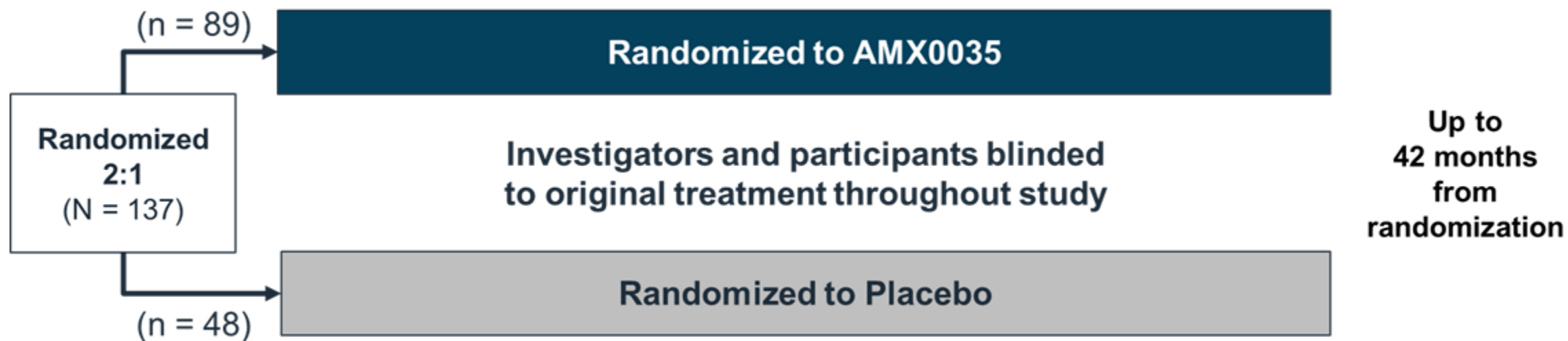
- Compares AMX0035 vs placebo

- From randomization to last participant, last visit (March 1, 2021)

- Survival captured for 136 / 137 participants

AMX0035 Results in Overall Survival Benefit in ITT Population

	Median Survival (Months)	Difference (Months)	Cox Regression Model HR (95% CI)	p-value
ITT AMX0035 (N = 89)	23.5	4.8	0.64 (0.4, 1.0)	0.045
Placebo (N = 48)	18.7			

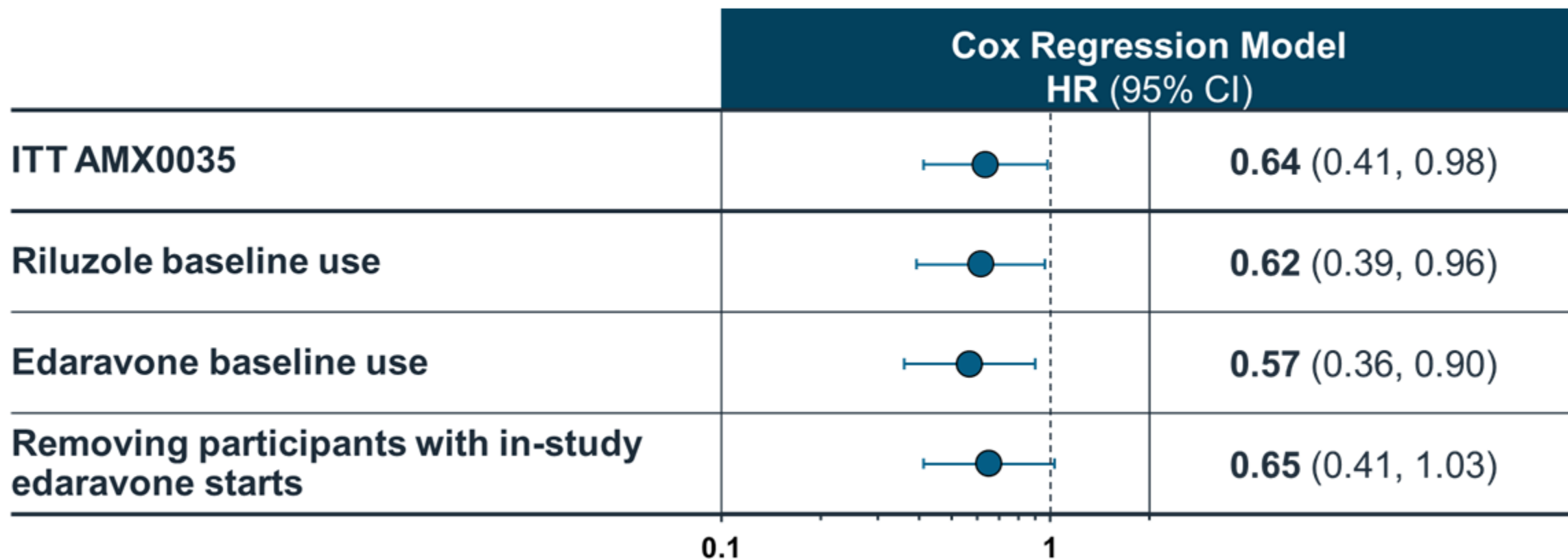# Longer Exposure to AMX0035 Associated with Longer Survival in Subgroup Analysis

Randomization Group	N	Mean Exposure to AMX0035 (Months)	Median Survival (Months, 95% CI)
Enrolled in Open-Label Phase			
AMX0035 + SOC	56	15.6	30.2 (24.9, NE)
Placebo + SOC	34	7.5	20.8 (17.2, 28.7)
Did Not Enroll in Open-Label Phase			
AMX0035 + SOC	33	2.7	17.4 (14.6, 23.1)
Placebo + SOC	14	0	15.2 (12.4, 24.9)

NE = Not Estimable

Groups Were Well-Balanced for Key Predictors of Survival

Baseline Characteristics	AMX0035 (N = 89) Mean (SD)	Placebo (N = 48) Mean (SD)
Time since symptom onset, months	13.5 (3.8)	13.6 (3.6)
ALSFRS-R pre-baseline slope	0.96 (0.42)	0.93 (0.60)
ALSFRS-R baseline	36 (5.7)	37 (5.1)
SVC, percent predicted	83% (19)	84% (16)
Age, years	57.9 (10.6)	57.3 (7.6)

Survival Prognosis Well-Balanced Between Groups

ITT OS Results Consistent Regardless of Riluzole and Edaravone Use

	Cox Regression Model HR (95% CI)	
ITT AMX0035		**0.64** (0.41, 0.98)
Riluzole baseline use		**0.62** (0.39, 0.96)
Edaravone baseline use		**0.57** (0.36, 0.90)
Removing participants with in-study edaravone starts		**0.65** (0.41, 1.03)

0.1   1

Concomitant Medication Use Did Not Impact Result

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)

0.1   1

Results Consistent Across Timepoints of Analysis

FDA Guidance Places Extra Weight on Critical Clinical Outcomes Such as Mortality

- **2017 FDA Guidance:** *"For many serious diseases, there is an endpoint of such great clinical importance that it is unreasonable not to collect and analyze the endpoint data; the usual example is* **mortality***... the* **suggestion** *of a favorable result on a major outcome such as mortality may be difficult to ignore."*

FDA Draft Guidance *Multiple Endpoints in Clinical Trials*, January 2017

New Analyses Support ITT OS

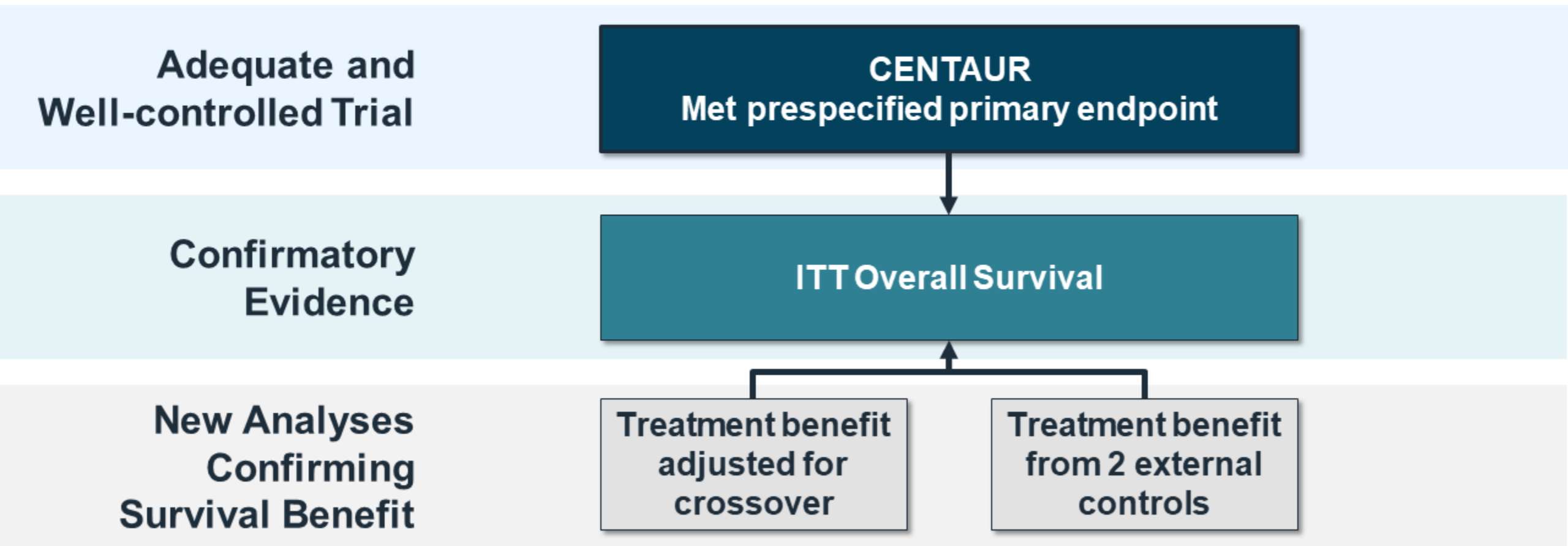|	
Adequate and Well-controlled Trial	**CENTAUR** **Met prespecified primary endpoint**
Confirmatory Evidence	**ITT Overall Survival**
New Analyses Confirming Survival Benefit	**Treatment benefit adjusted for crossover** **Treatment benefit from 2 external controls**

Additional Overall Survival Analyses Support Robustness of ITT OS Analysis

- Three new analyses used 3 different control arms; 2 external to trial
  - Placebo arm adjusted for crossover
  - External Control #1: Predicted survival control arm
  - External Control #2: Propensity score-matched historical clinical trial control arm
- Independent and consistent evidence of meaningful benefit

New Analyses Support Robustness of ITT OS Result
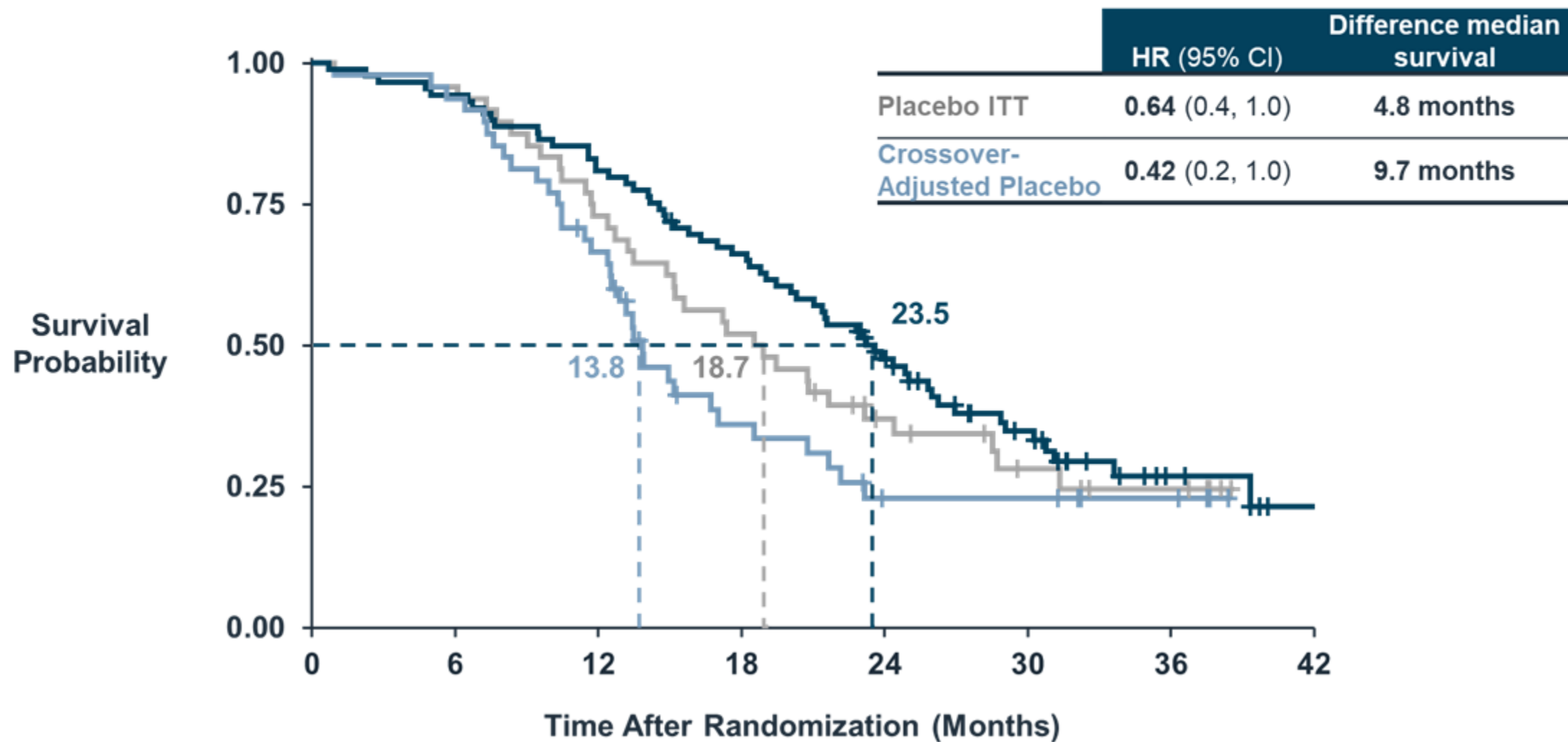
Placebo Arm Adjusted for Crossover
Rank Preserving Structural Failure Time Model (RPSFTM)

- Estimates OS for placebo arm in the absence of treatment switching[1,2]

  - Calculate survival time gained by receiving active treatment

  - Frequently used model in oncology

- Extensive supporting literature and cited in FDA drug reviews and health technology assessments[3-5]

- Comparison groups

  - **Observed** AMX0035 survival

  - Placebo arm **adjusted** for crossover survival

1. Jönsson, 2014; 2. Latimer, 2014; 3. Hussain, 2020; 4. Turner, 2018; 5. Zhu, 2021

Adjusting Placebo Arm for Crossover Demonstrated Significant OS Benefit

	Median Survival (Months)	Difference (Months)	Cox Regression Model HR (95% CI)	p-value
Observed ITT AMX0035 (N = 89)	23.5	9.7	0.42 (0.2, 1.0)	0.045
Placebo adjusted for crossover (N = 48)	13.8			

Adjusting Placebo Arm for Crossover Demonstrated Significant OS Benefit

	HR (95% CI)	Difference median survival
Placebo ITT	**0.64** (0.4, 1.0)	**4.8 months**
Crossover-Adjusted Placebo	**0.42** (0.2, 1.0)	**9.7 months**

Survival Probability

Time After Randomization (Months)

Paganoni et. al., 2022 Supplementary Appendix

RPSFTM Analysis Addresses Placebo Cross-Over

Placebo Arm Adjusted for Crossover

- Estimates treatment-naïve placebo arm using well-supported methodology
    - Follows rigorous approaches cited in FDA guidance, papers in NEJM and JAMA, and utilized in past reviews[1-5]
- Assumes common treatment effect
    - Reasonable given only 6-month before crossover
- In Latimer et al. simulation study, maximum bias < 10%[2]
- P-value pulled from ITT overall survival result[2]

1. Jönsson, 2014; 2. Latimer, 2014; 3. Hussain, 2020; 4. Turner, 2018; 5. Zhu, 2021

Using Appropriate External Controls in ALS Studies

- Using external controls can bolster confidence in RCT result, such as OS benefit observed in CENTAUR

> **2019 FDA Guidance:** *"For example, a single trial showing marked improvement in survival compared to a control group, either **external to the trial** or concurrent, could be supported by data from separate sources (e.g., **a natural history study**, case report forms, or registries) that demonstrate a very limited median survival time or other clinically highly important outcome without treatment. **In this case, the natural history data would represent confirmatory evidence.**"*

- Critical that external control is appropriate and well-matched
  - Use 2 most robust ALS data sources for survival comparison
    - **E**uropean **N**etwork to **C**ure **ALS** (**ENCALS**) survival prediction model
    - **P**ooled **R**esource **O**pen-Access **A**LS **C**linical **T**rials Database (**PRO-ACT**)

Independent External Control #1: Natural History Survival Prediction Model

- Validated natural history prediction model from > 10,000 people with ALS in Europe
- Developed and validated model
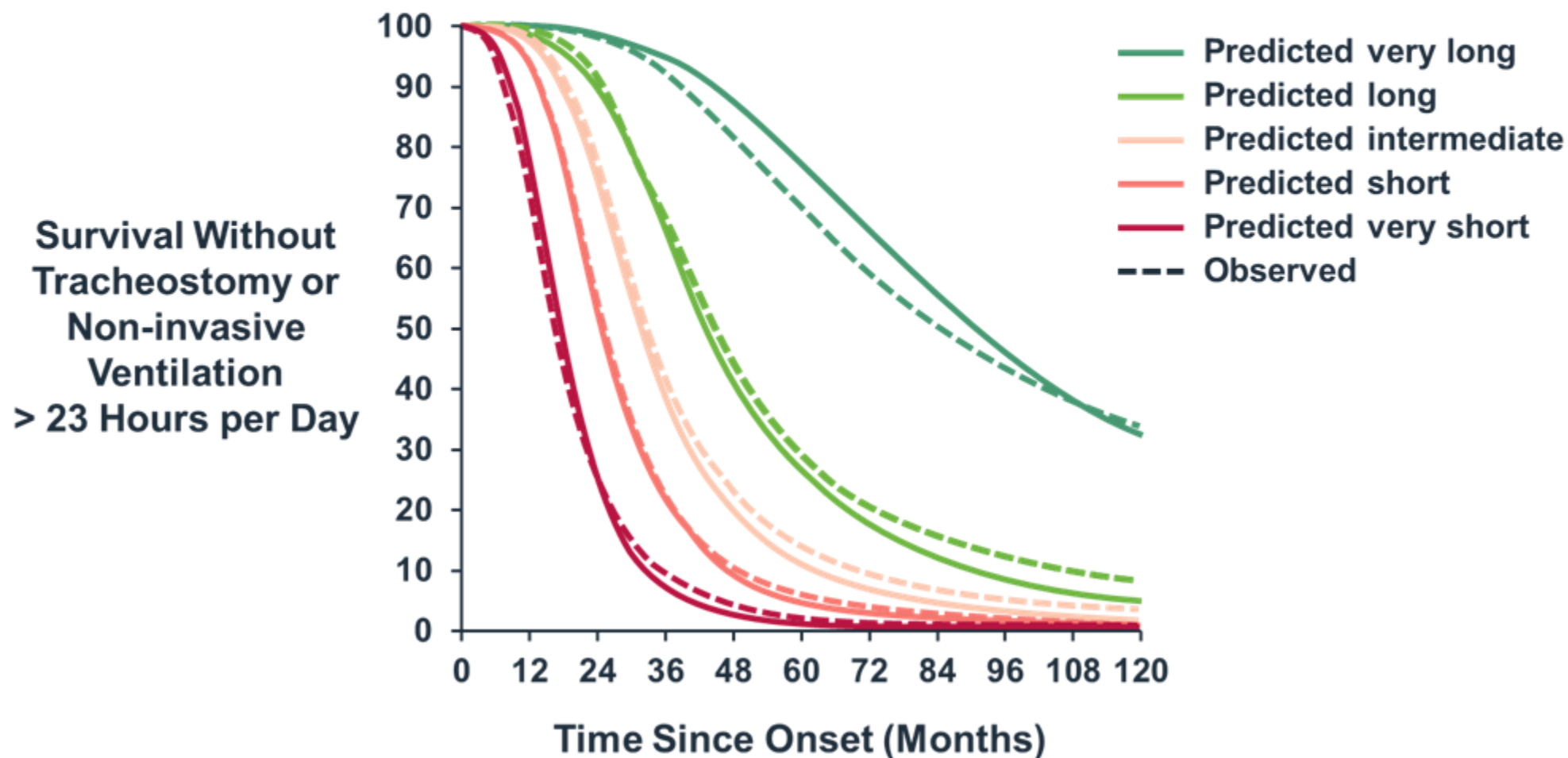 - Clinical, cognitive, and genetic predictors of tracheostomy-free survival

Predictors*

- Bulbar vs non-bulbar onset
- Age at onset
- Definite vs probable or possible ALS
- Diagnostic delay
- Forced vital capacity
- Pre-study progression rate
- Frontotemporal dementia**
- Presence of *C9orf72* repeat expansion**

*All predictors $p < 0.0001$
**Data not available in CENTAUR population; sensitivity analyses show accurate predictions when these 2 factors are missing

Westeneng et al, 2018

Survival Predictions from Model Align to Observed Survival in Validation Cohort

Survival Without Tracheostomy or Non-invasive Ventilation > 23 Hours per Day

Legend:
- Predicted very long
- Predicted long
- Predicted intermediate
- Predicted short
- Predicted very short
- --- Observed

X-axis: Time Since Onset (Months)
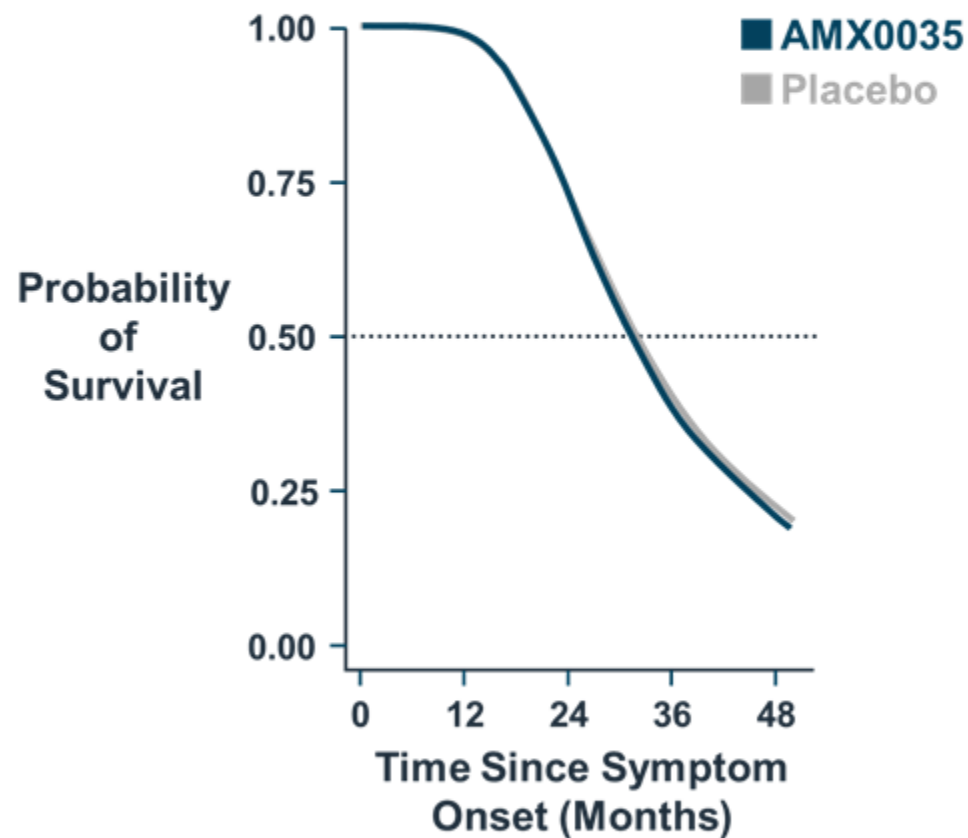
Westeneng et al, 2018

Model Used to Generate Predicted Survival

- Generated predicted survival for each participant in CENTAUR
  - Originators blinded to original treatment assignments

Comparison groups

1 **Predicted** AMX0035 survival at baseline

Predicted placebo survival at baseline

Similar Predicted Survival at <u>Baseline</u> for AMX0035 and Placebo Groups in CENTAUR

Survival Prognosis Well-Balanced Between Groups at Baseline

Model Used to Generate Predicted Survival

- Generated predicted survival for each participant in CENTAUR
  - Originators blinded to original treatment assignments

Comparison groups

1 ENCALS AMX0035 predicted survival at baseline
ENCALS placebo predicted survival at baseline

2 **Observed** AMX0035 survival
Predicted AMX0035 survival

Natural History Model Provides Additional Supportive Evidence of ITT OS Results

- AMX0035 showed prolonged OS vs natural history predicted control

	Median Survival (Months)	Difference (Months)	Hazard Ratio (95% CI)	p-value
Observed ITT AMX0035 (N = 89)	23.5			
Natural history survival prediction control (N = 89)	13.6	9.9	0.32 (0.2, 0.4)	< 0.0001

Natural History Model Provides Additional Supportive Evidence of ITT OS Results

Statistic	
Difference Median Survival	9.9 months
HR (95% CI)	0.32 (0.2, 0.4)
p-value	< 0.0001
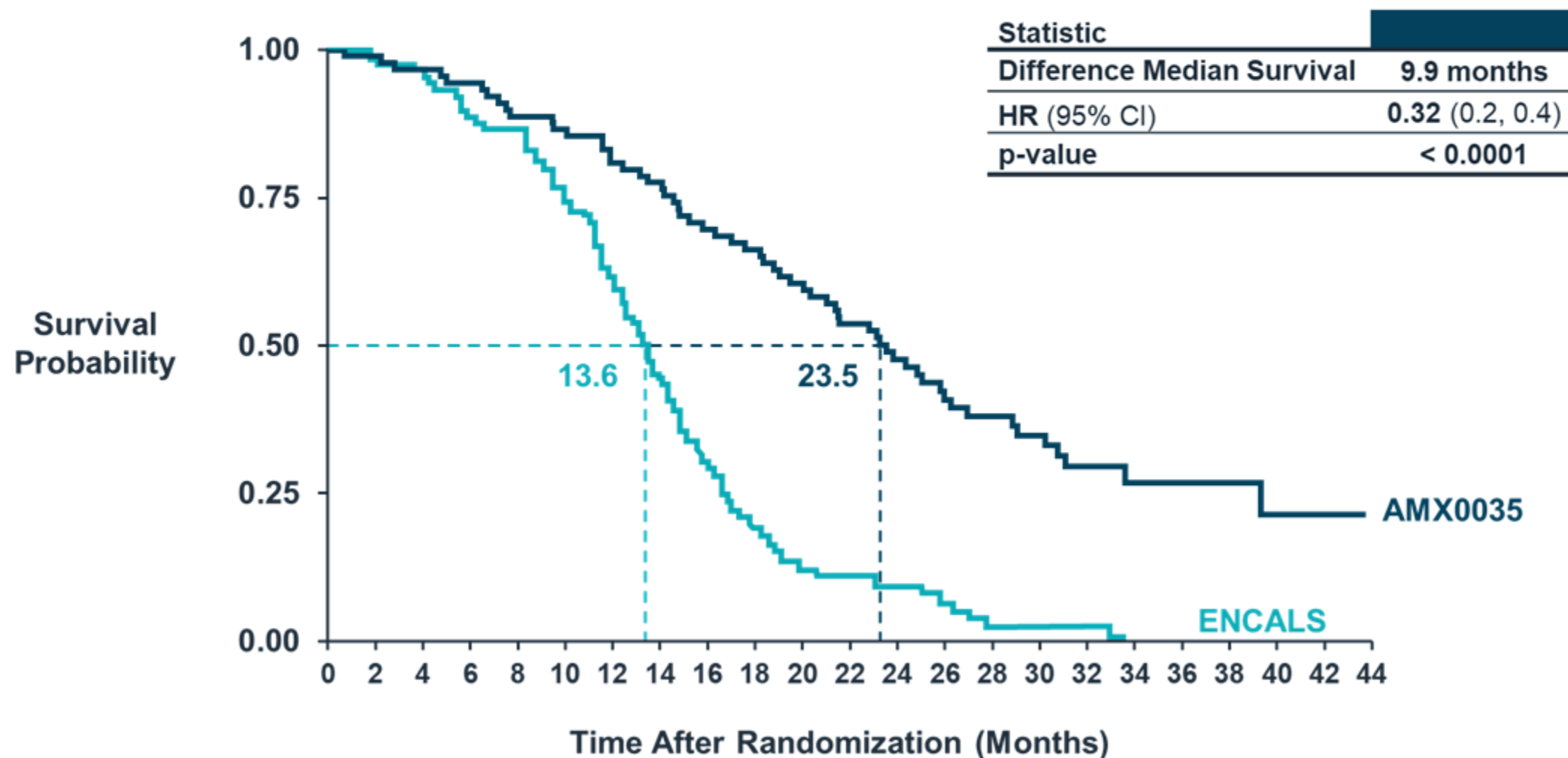
Natural History Survival Prediction Model Analysis Supports ITT OS Result with External Data

External Control #1: Natural History Survival Prediction Model

- Treatment-naïve comparator arm
- Natural history data specified as confirmatory evidence
- Consistent survival benefit using new data external to CENTAUR
- Limitations in terms of population match
  - European, clinic-based population

Independent External Control #2: Historical Clinical Trial Comparator

- Largest database (> 11,000) of de-identified ALS clinical trial participants[1,2]

  - Mostly US clinical trial data

- NEALS clinical trial consortium – overlapping sites in PRO-ACT and CENTAUR

- Comparison groups

  - **Observed** AMX0035 survival

  - Propensity score matched **historical clinical trial control**

1. Atassi, 2014; 2. PRO-ACT website

Historical Clinical Trial External Control Arm Met Key CENTAUR Entry Criteria

- Control participants from historical trials

- Baseline and ≥ 1 post-baseline ALSFRS-R score

- Meet major inclusion / exclusion from CENTAUR at baseline in PRO-ACT
  - Between 18-80 years old
  - Definite ALS diagnosis El Escorial criteria
  - ≤ 18 months since ALS symptom onset
  - Predicted VC > 60% (FVC or SVC used whichever available)

- Known mortality information
  - Either known death date or known alive at end of follow-up
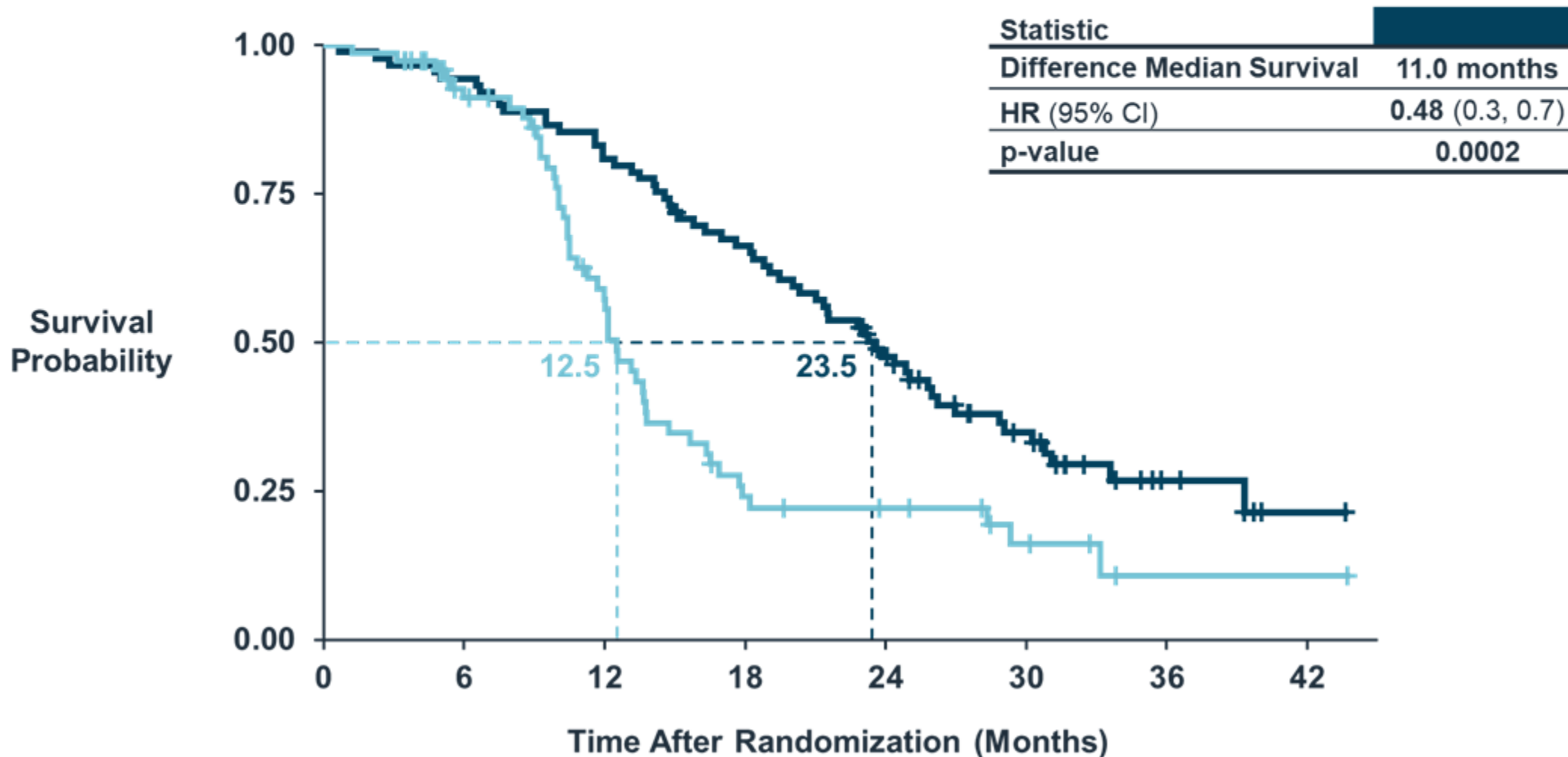
Propensity Score Matching Used on Control Arm

- Propensity score was calculated using key prognostic covariates
- 74 had propensity score match with AMX0035 group

Covariates	AMX0035 ITT (N = 89)		Historical Clinical Trial Control (N = 74)	
	Mean (SD)	Range	Mean (SD)	Range
Time since symptom onset, months	13.6 (3.8)	3.0, 20.0	12.3 (3.4)	3.6, 17.6
ALSFRS-R pre-baseline slope	0.96 (0.42)	0.12, 1.94	0.95 (0.57)	0.14, 3.14
SVC / FVC, percent predicted	83% (19)	38, 142	84% (14)	60, 131
Age, years	57.9 (10.6)	31, 79	57.5 (10.0)	32, 77

Historical Clinical Trial Control Arm Demonstrates Significant OS Benefit

	Median Survival (Months)	Difference (Months)	Cox Regression Model HR (95% CI)	p-value
Observed ITT AMX0035 (N = 89)	23.5			
		11.0	0.48 (0.3, 0.7)	0.0002
Historical clinical trial control (N = 74)	12.5			

Historical Clinical Trial Control Arm Demonstrates Significant OS Benefit

Statistic	
Difference Median Survival	11.0 months
HR (95% CI)	0.48 (0.3, 0.7)
p-value	0.0002

Historical Clinical Trial Control Arm Supports ITT OS Result with External Data

Propensity Score Matched Historical Clinical Trial Control Arm

- Treatment-naïve comparator arm
- Propensity score matching cited in FDA Real World Evidence Framework
- Consistent survival benefit using new data external to CENTAUR trial
- Addresses some limitations from natural history survival prediction model in terms of population match
  - US, clinical-trial population with overlapping NEALS sites
  - Propensity score matched

AMX0035 Survival Benefit Provides Confirmatory Evidence of Efficacy

Analysis Method	Control Group Median OS (Months)	AMX0035 Median OS (Months)	Difference (Months)	Hazard Ratio (95% CI)	p-value
ITT OS	18.7	23.5	4.8	0.64 (0.4, 1.0)	0.045
New Survival Analyses with Different Control Groups					
Crossover-adjusted placebo arm comparison	13.8	23.5	9.7	0.42 (0.2, 1.0)	0.045
Natural history survival prediction external control arm comparison	13.6	23.5	9.9	0.32 (0.2, 0.4)	< 0.0001
Propensity score matched historical clinical trial external control arm comparison	12.5	23.5	11.0	0.48 (0.3, 0.7)	0.0002

Three Control Groups Yield Consistent Support for ITT OS Result
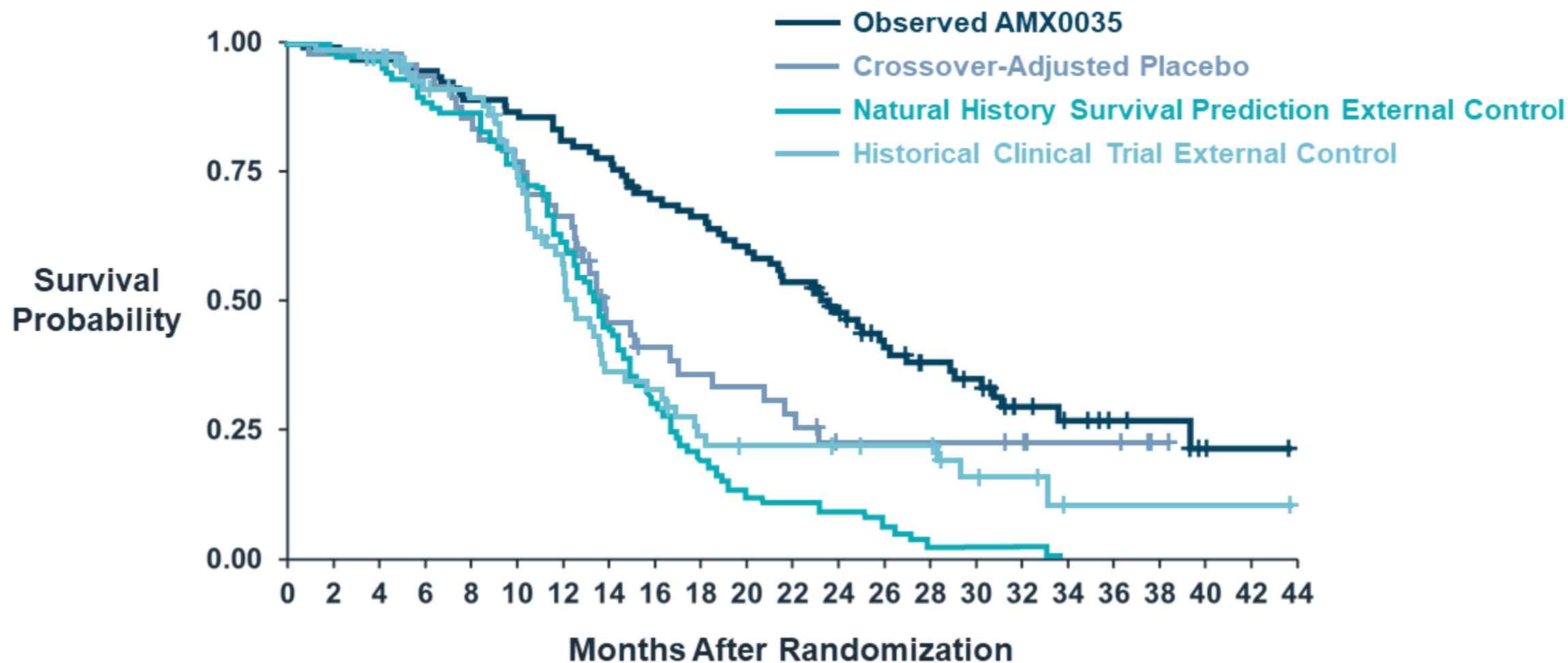
Single Adequate and Well-Controlled Study Plus Confirmatory Evidence Constitute Substantial Evidence of Effectiveness for AMX0035

Pathway for Demonstrating Clinical Effectiveness from Single Pivotal Study	Difference	p-value
Adequate well-controlled study, ALSFRS-R	2.3 points	0.034
Confirmatory evidence, OS ITT	4.8 months	0.045
Crossover-adjusted placebo arm	9.7 months	
Natural history survival prediction external control	9.9 months	< 0.0001
Propensity score matched historical clinical trial external control	11.0 months	0.0002

Clinical Perspective

Merit E. Cudkowicz, MD, MSc

Chief, Neurology Department
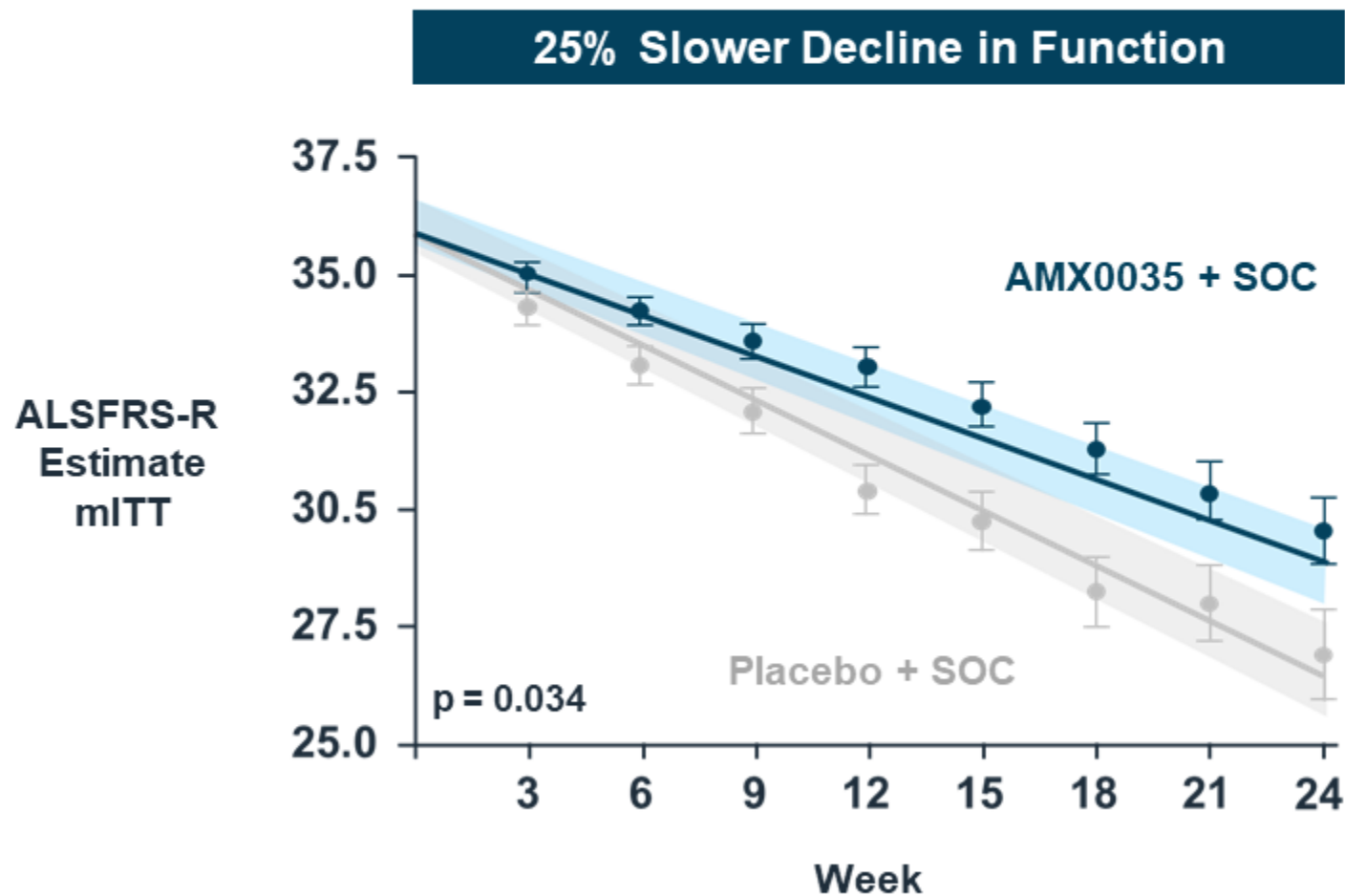
Massachusetts General Hospital

Director, Sean M. Healey & AMG Center for ALS

Julieanne Dorn Professor of Neurology,

Harvard Medical School

Functional Benefits Observed Are Highly Meaningful

25% Slower Decline in Function

ALSFRS-R Estimate mITT

AMX0035 + SOC

Placebo + SOC

p = 0.034

Week

SOC = Standard of Care

Robust and Meaningful Survival Benefit with AMX0035

	Median Overall Survival Benefit	p-value
ITT OS	4.8 months	0.045
Supportive Survival Analyses		
Crossover-adjusted placebo arm	9.7 months	0.045
Natural history external control	9.9 months	< 0.0001
Historical clinical trial external control	11.0 months	0.0002

- Review in *JAMA* of all oncologic drugs approved between 2000 and 2016 showed median OS benefit 2.4 months (HR = 0.77)[1]
- AMX0035 shows 4.8 months (HR = 0.64)

1. Ladanie, 2020

CENTAUR – First and Only Trial to Show Benefit on Both Function and Survival

- ALS is an exceptionally challenging disease to study and measure in clinical studies
    - Majority of all ALS trials failed
- Personally involved in 38 ALS clinical trials
    - 4 trials had positive biomarker findings but did not meet prespecified primary endpoint
    - 2 met their primary endpoint (AMX0035 and Nuedexta®)
    - 1 (AMX0035) showed positive results on both primary functional result and survival
- CENTAUR designed and executed by experts

Positive Benefit / Risk Supports Use of AMX0035

- AMX0035 slows progression and extends life with no significant safety concerns

- CENTAUR results and confirmatory evidence provide more than sufficient evidence to support approval

- People living with ALS should have access now to AMX0035
  - Uniformly fatal, rapid illness

Generation of People Living with ALS Impacted by This Decision
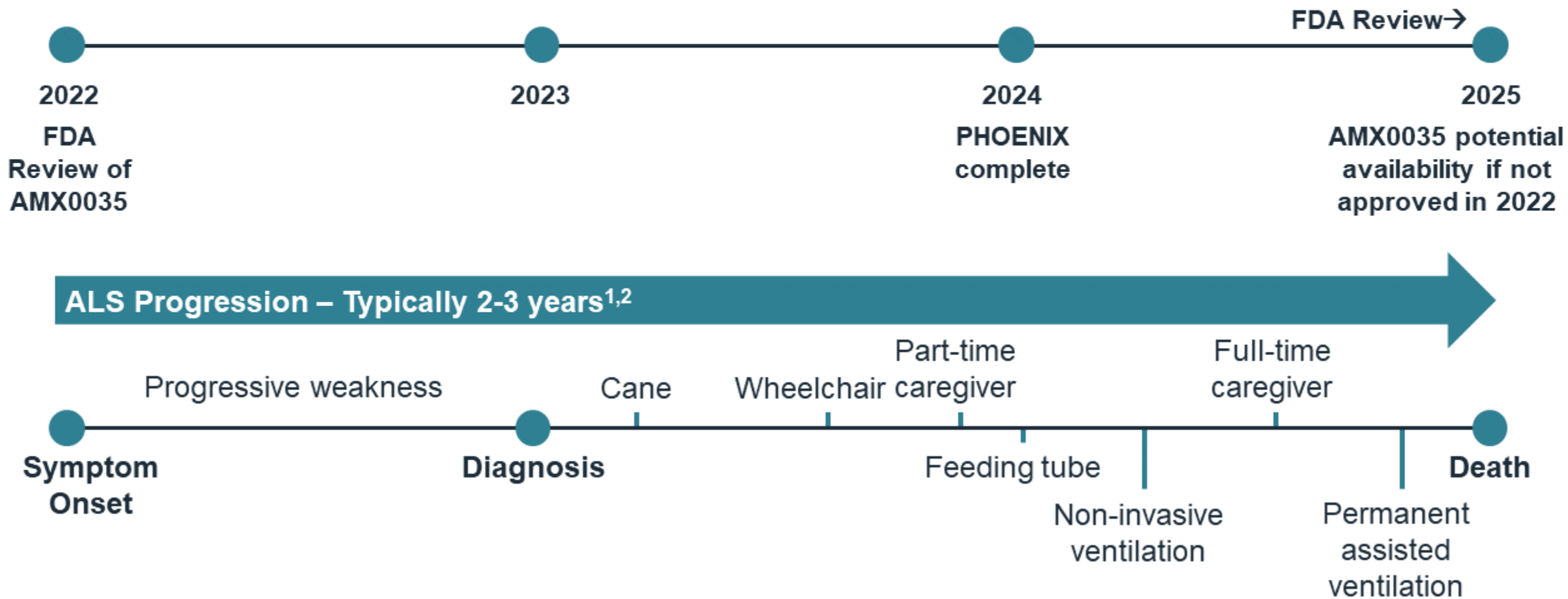
2022
FDA Review of AMX0035

2023

2024
PHOENIX complete

FDA Review→

2025
AMX0035 potential availability if not approved in 2022

ALS Progression – Typically 2-3 years[1,2]

Progressive weakness

Cane

Part-time
Wheelchair caregiver

Full-time caregiver

Symptom Onset

Diagnosis

Feeding tube

Non-invasive ventilation

Permanent assisted ventilation

Death

1. Paganoni, 2014; 2. Chiò, 2009

AMX0035

September 07, 2022

Amylyx Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee

BACKUP SLIDES SHOWN

RCP Weeks 0-24: AMX0035 Treatment Showed Consistent Effect Across Subgroups

	AMX0035	Placebo	ALSFRS-R Estimate (95% CI)	
Age (Years)				
≤ 59	44	31		2.8 (-0.2, 5.8)
> 59	43	17		3.7 (-0.1, 7.4)
Sex				
Female	26	16		0.8 (-3.0, 4.5)
Male	61	32		4.0 (1.1, 6.8)
History of ALS				
Familial	9	7		6.3 (-4.3, 16.8)
Sporadic	76	38		2.7 (0.3, 5.1)

-10 -8 -6 -4 -2 0 2 4 6 8 10

Favors Placebo ◀▶ Favors AMX0035
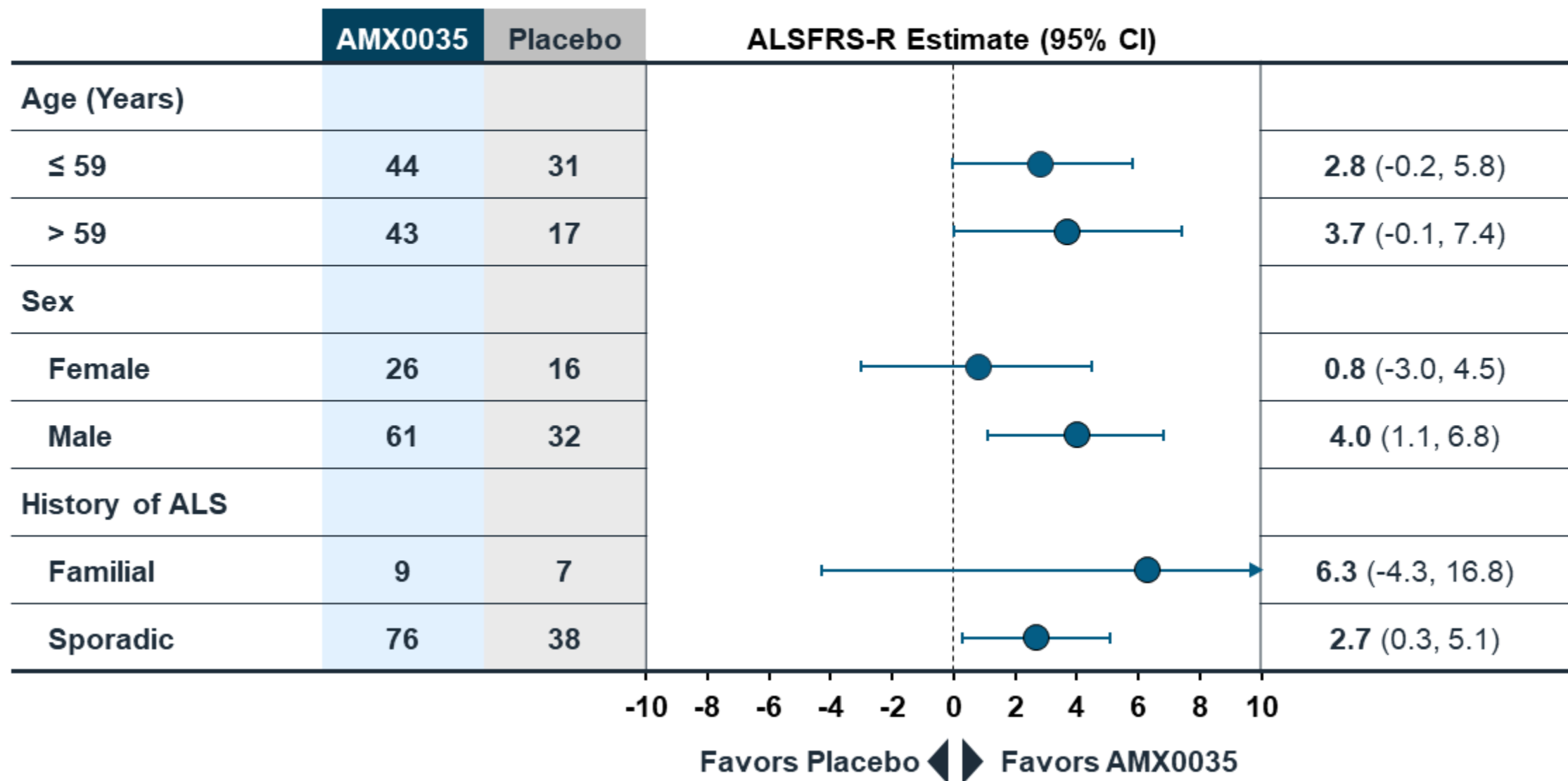
Actual Placebo Progression Matches Propensity Score Matched PRO-ACT Historical Control

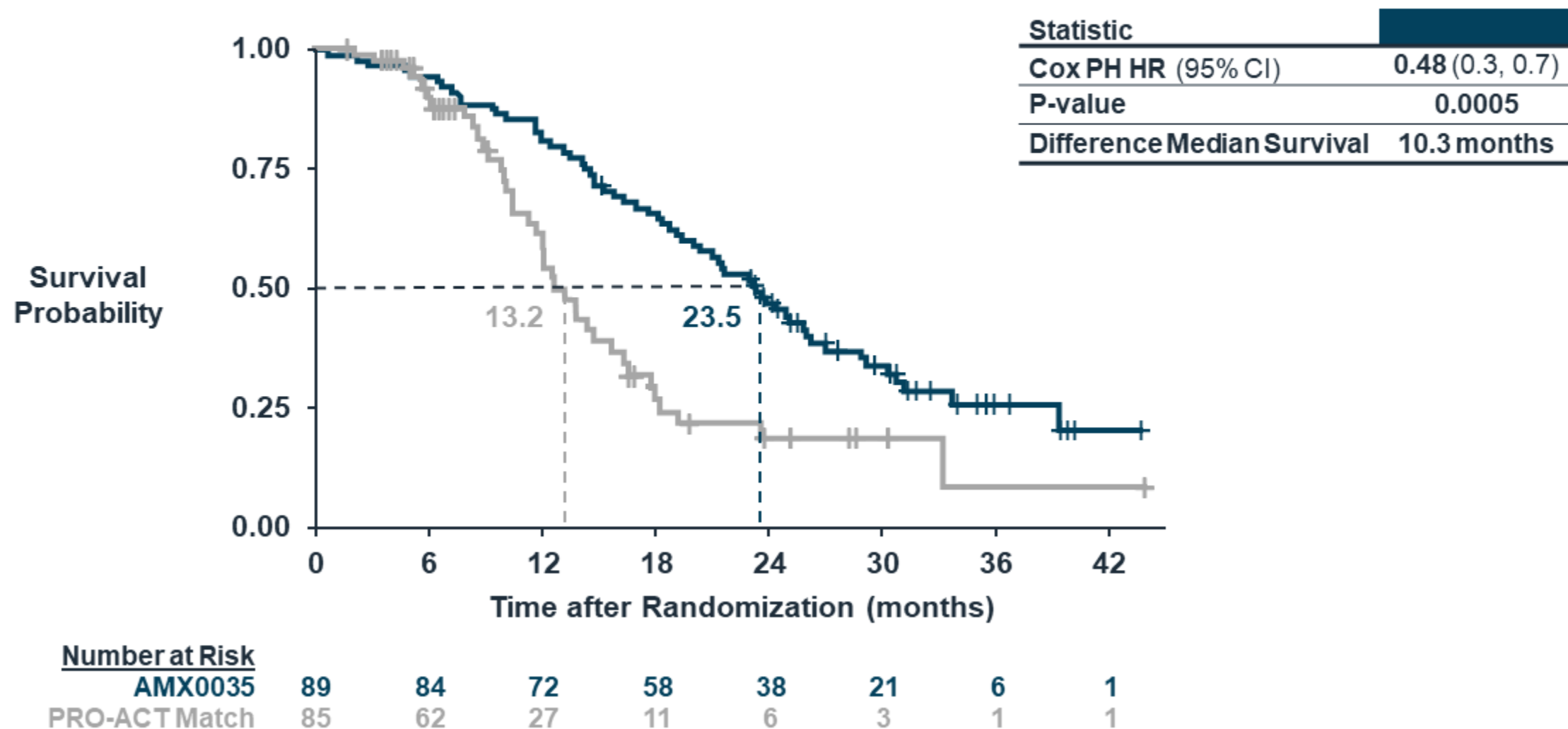|	AMX0035 (N = 87)	Placebo (N = 48)	PRO-ACT Matched (N = 74)
ALSFRS-R Progression Rate 0-24 Weeks (points per month)	-1.24	-1.66	-1.69

Updated PRO-ACT Analysis
Consistent Overall Survival Benefit for AMX0035

Statistic	
Cox PH HR (95% CI)	**0.48** (0.3, 0.7)
P-value	0.0005
Difference Median Survival	10.3 months

Survival Probability

13.2   23.5

Time after Randomization (months)

Number at Risk

AMX0035	89	84	72	58	38	21	6	1
PRO-ACT Match	85	62	27	11	6	3	1	1

Treatment-Naïve Subgroup Aligns with PRO-ACT Predictions

RCP: Adverse Events Similar Between Arms, Majority Mild or Moderate

	AMX0035 + SOC (N = 89)	Placebo + SOC (N = 48)
Any AE	86 (97%)	46 (96%)
Severe AE	17 (19%)	11 (23%)
SAE	11 (12%)	8 (17%)
AE leading to discontinuation of study drug	18 (20%)	5 (10%)
Death	5 (6%)	2 (4%)

Primary Endpoint Results Are Robust Across Sensitivity Analyses

ALSFRS-R Analysis	On Con Med	Difference (95% CI)	p-value
Primary Outcome		2.3 (0.2, 4.5)	0.034
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
Remove participants with in-study edaravone starts		2.4 (0.1, 4.7)	0.041
Adjusted for baseline edaravone use	YES	2.6 (0.4, 4.8)	0.023
Adjusted for baseline edaravone use	NO	2.5 (0.3, 4.6)	0.027
Adjusted for baseline riluzole use	YES	2.9 (0.7, 5.1)	0.011
Adjusted for baseline riluzole use	NO	2.3 (0.1, 4.5)	0.041

Use of Concomitant medications

-2 0 2 4 6

Favors Placebo ◀ ▶ Favors AMX0035