Long-Term Survival of Participants in the CENTAUR Trial of AMX0035 for ALS: Outcomes and Novel Approaches

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MGH 1811

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Disclosures

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AMX0035 is an investigational product, and AMX0035 has not been determined to be safe and effective by the FDA or other health authorities (e.g., EMA and Health Canada). This presentation is intended to provide scientific information about AMX0035.

AMX0035 Background

AMX0035 is a Fixed-Dose Co-Formulation of the Compounds PB and TURSO[1]

CENTAUR

Combination of

Ph**EN**ylbutyrate (PB)

and **TAUR**sodiol (TURSO)

AMX0035 is designed to reduce neuronal death by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction[1]

PB and TURSO, individually, have shown activity in preclinical models of neurodegenerative diseases, including ALS[2-4]

In combination, PB and TURSO have been shown to attenuate neuronal death and other pathology in cell cultures[5]

Study Drug Administration

- Dissolved in water and administered **by mouth or via feeding tube**
- Taken once daily for first 3 weeks, then twice daily if tolerating
- Placebo matched for appearance, taste, and solubility

1. Paganoni S, et al. *New Eng J Med*. 2020. **2.** Rodrigues CM, et al. *Biochemistry*. 2003;42(10):3070-3080. **3.** Cho JA, et al. *PLoS One*. 2014;9(11)e110086. doi: 10.1371/journal.pone.0110086.
4. Ryu H. *J Neurochem*. 2005;93(5):1087-1098. **5.** Cohen J, et al. Poster presented at: 28th International Symposium for ALS/MND; December 4-10, 2017; Boston, MA.

The CENTAUR Trial Was Done in Partnership With the ALS Community

CENTAUR

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute®

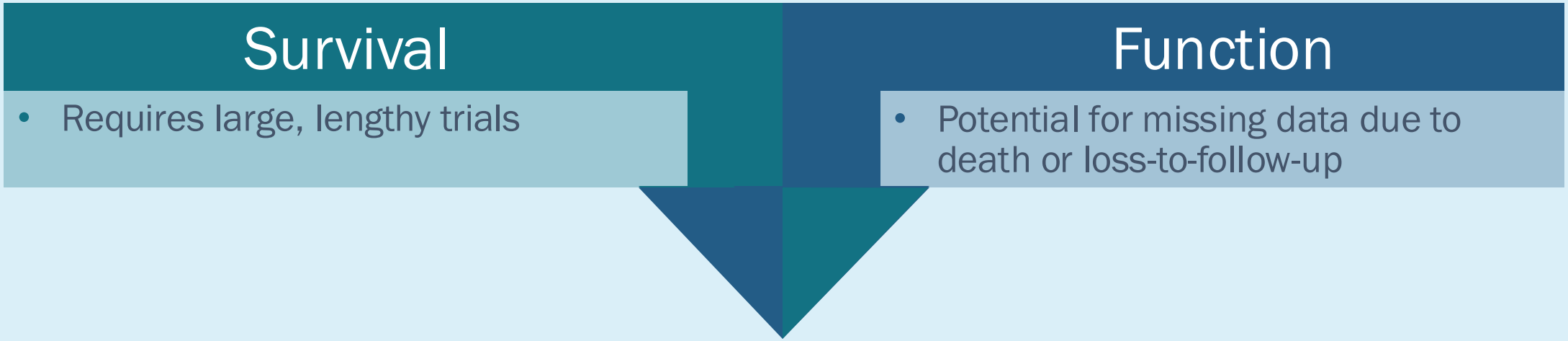
ALS ASSOCIATION

alsFINDINGaCURE®

AMYLYX

CENTAUR Design

Primary Efficacy Endpoints in ALS Clinical Trials[1,2]



Both are important measures of disease progression and response to therapy for clinicians and individuals with ALS

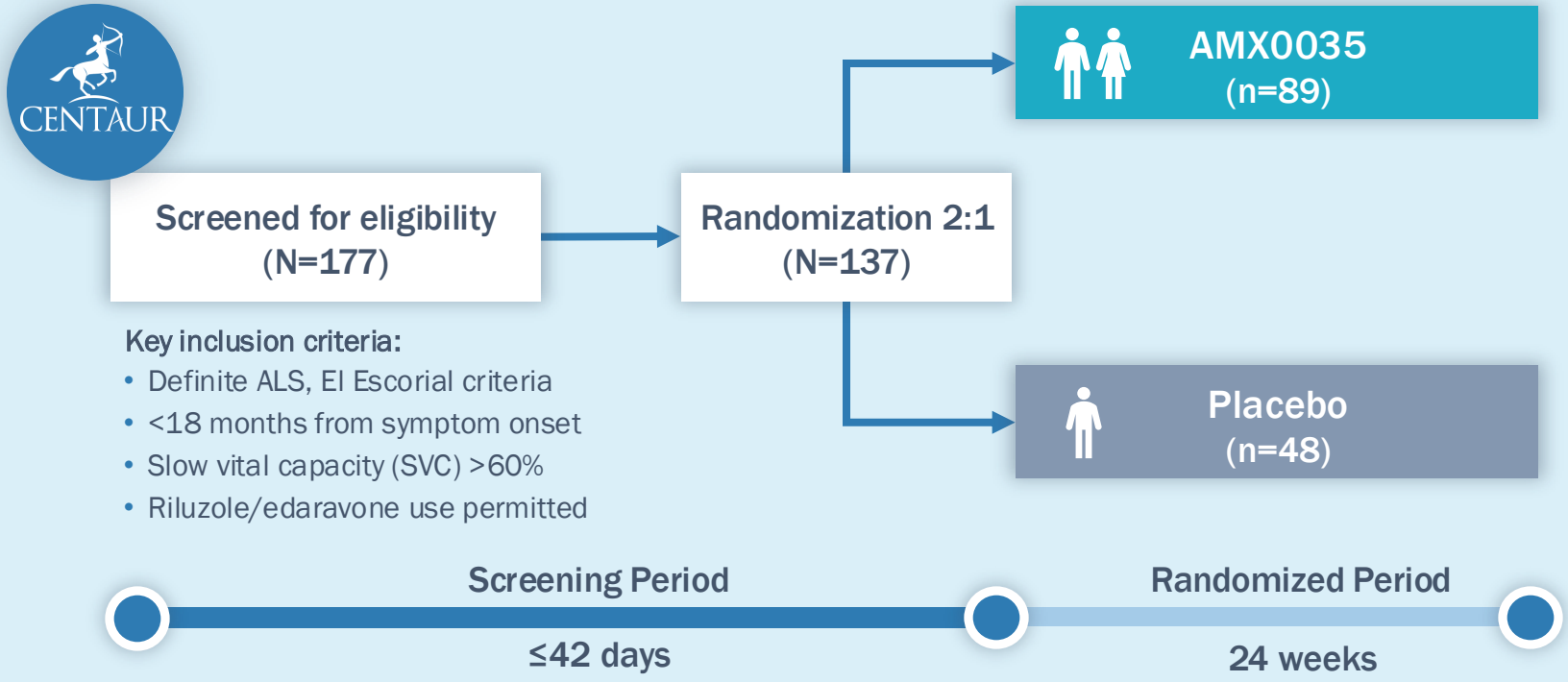
This presentation will discuss novel approaches to gather meaningful survival data despite a 6-month randomized period

1. Berry, JD et al. *Amyotroph Lateral Scler Frontotemporal Degen*. 2013;14(3):162-168. **2.** van Eijk RP, et al. Clin Epidemiol. 2018;10:333-341.

CENTAUR Randomized Period

Primary objectives:

- To determine the **safety** and **tolerability** of AMX0035
- To measure the **impact of AMX0035 on ALSFRS-R slope**



Primary Efficacy Endpoint

- ALSFRS-R

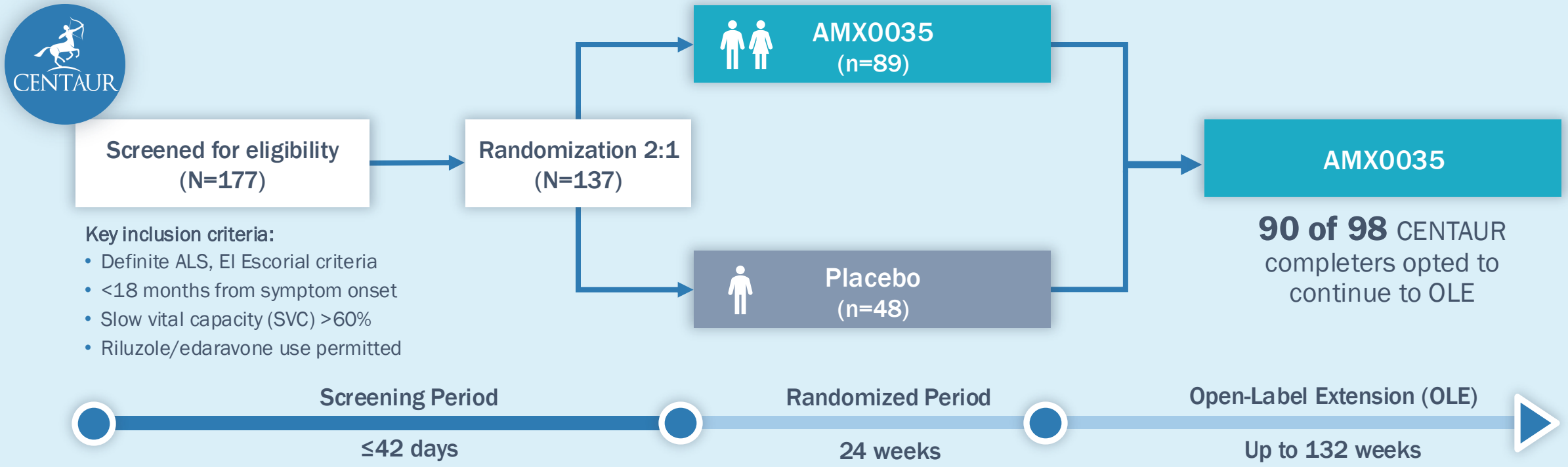
Secondary Efficacy Endpoints

- The Accurate Test of Limb Isometric Strength (ATLIS)
- Neurofilament Heavy Chain (pNF-H)
- Slow vital capacity (SVC)
- Time to death, tracheostomy, or permanent assisted ventilation (PAV)*
- Time to death, tracheostomy, PAV,* or any hospitalization

*Permanent assisted ventilation (>22 hours daily for >7 days)

Paganoni S, et al. *N Engl J Med*. 2020;383:919-930.

CENTAUR Randomized Period and Open Label Extension[1,2]



1. Paganoni S, et al. *N Engl J Med*. 2020;383:919-930. **2.** Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091

Baseline Characteristics

Characteristic	AMX0035 (n=89)	Placebo (n=48)
Age (y), mean (SD)	57.9 (10.6)	57.3 (7.6)
BMI (kg/m^2), mean (SD)	26.9 (4.4)	26.4 (5.8)
Pre-baseline ALSFRS-R slope (points/mo), mean (SD)	0.96 (0.4)	0.93 (0.6)
Months since ALS diagnosis, mean (SD)	5.9 (3.3)	6.3 (3.2)
Months since ALS symptom onset, mean (SD)	13.5 (3.8)	13.6 (3.6)
Edaravone or riluzole use at or prior to study entry, n (%)	64 (72)	42 (88)
Edaravone use	23 (26)	24 (50)
Riluzole use	61 (68)	37 (77)
Use of both	20 (22)	19 (40)
Bulbar onset, n (%)	26 (29)	10 (21)
SVC (% predicted), mean (SD)	82.7 (19.0)	83.9 (15.9)
Mean ALSFRS-R total score, mean (SD)	35.6 (5.7)	36.7 (5.1)
ATLIS total score (% predicted), mean (SD)	56.4 (20.0)	53.9 (20.9)
ATLIS upper extremity score (% predicted), mean (SD)	54.7 (24.2)	51.4 (25.2)
ATLIS lower extremity score (% predicted), mean (SD)	56.9 (25.1)	57.1 (25.8)

Mean age
57

Mean time from symptom onset
13.5 months

Mean time from diagnosis
6 months

Bulbar onset
26%

On riluzole or edaravone at or prior to study entry
77%

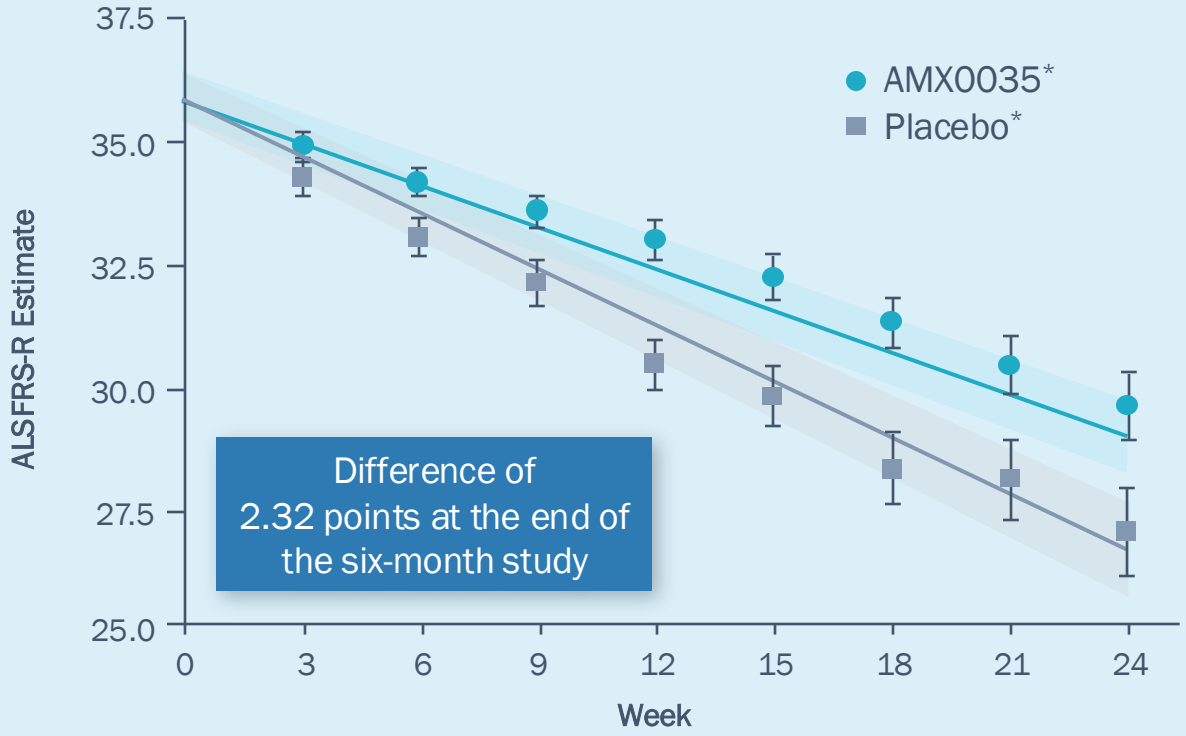
Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091

CENTAUR Randomized Period

CENTAUR Randomized Period: Summary

Function

Primary Endpoint: ALSFRS-R Total



*77% of participants were on riluzole or edaravone at or prior to study entry. AMX0035 effect on primary outcome was consistent regardless of baseline use of concomitant medications

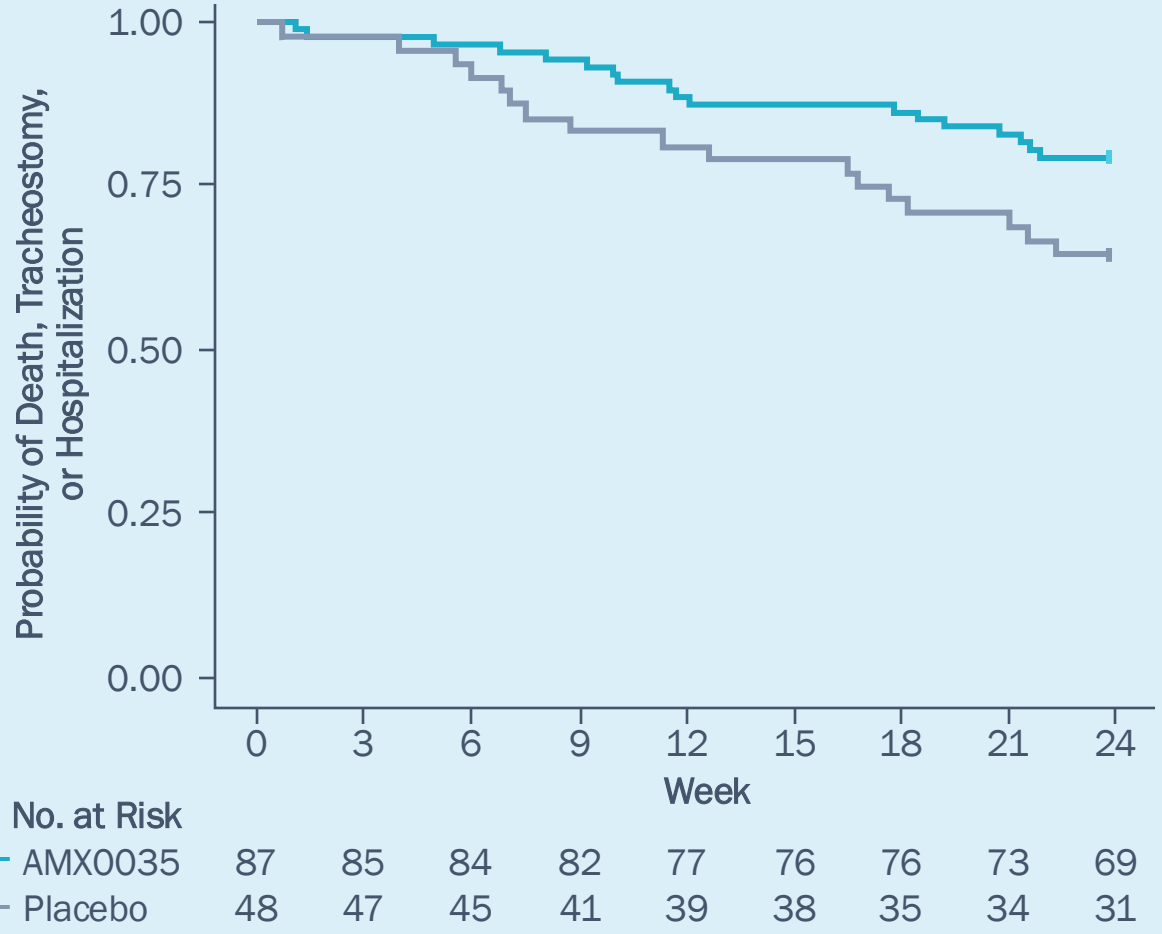
Safety

Similar rates of adverse events were recorded in the AMX0035 and placebo groups during the 24-week randomized period

- Events that occurred with greater (≥2%) frequency in the AMX0035 group were primarily GI

Paganoni S, et al. *NEJM*. 2020;383:919-930.

CENTAUR Randomized Period: Death, Tracheostomy, and Hospitalizations



The cumulative hazard ratio for death, tracheostomy, or hospitalization in the AMX0035 group, as compared with the placebo group, was 0.53 (95% CI: 0.27–1.05)

The adjusted risks of death, tracheostomy, and hospitalization were not significantly different between active treatment and placebo groups ($P = 0.07$)

Data censored at time of end of follow-up in trial. There were no instances of PAV delivered by non-invasive means in the study.

Paganoni S, et al. *N Engl J Med*. 2020;383:919-930.

Post-Hoc Joint-Rank Analysis

- Joint rank test performed as an integrated analysis of function and survival
  - ITT population
  - Covariates del-FS and age
- Showed no bias in the estimate of the primary functional outcome by loss of data due to participant death. Results remained statistically significant
  - 16.56 rank difference between AMX0035 and placebo groups, ***P*= 0.014**

1. Paganoni S, et al. *N Engl J Med*. 2020;383:919-930. **2.** Data on File. Amylyx Pharmaceuticals. **3.** Berry, JD et al. *Amyotroph Lateral Scler Frontotemporal Degen*. 2013;14(3):162-168.

Overall Survival

Novel Approaches

Challenge	Solution
The CENTAUR trial was designed to detect a significant difference in disease progression (ALSFRS-R) between AMX0035 and placebo groups in the shortest time possible – Even in a rapidly progressing ALS population, six months was not enough to detect a difference in survival	Assess long-term survival in ALL participants using a participant locating service

Methods Overview

Cut-off date of **July 20, 2020**

(longest follow-up, **35 months after randomization**)

A search of public records by OmniTrace successfully confirmed vital status for all but **2** (135/137) participants as of July 2020[a]

As of July 2020, participants had varying durations of follow-up post-randomization and are **censored** at the point they no longer have data

In this analysis, all participants were still alive at the time of censoring

[a] The 2 participants that could not be confirmed as of July 2020 were censored at the date of last contact with their clinical site

Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091

Overall Survival Analysis

Prespecified survival analysis compared time to death (all-cause mortality) for **every participant randomized in CENTAUR**, including those who withdrew, were lost to follow-up, or did not enroll in the OLE

Participants originally randomized to AMX0035 (N=89)

Participants originally randomized to placebo (N=48)

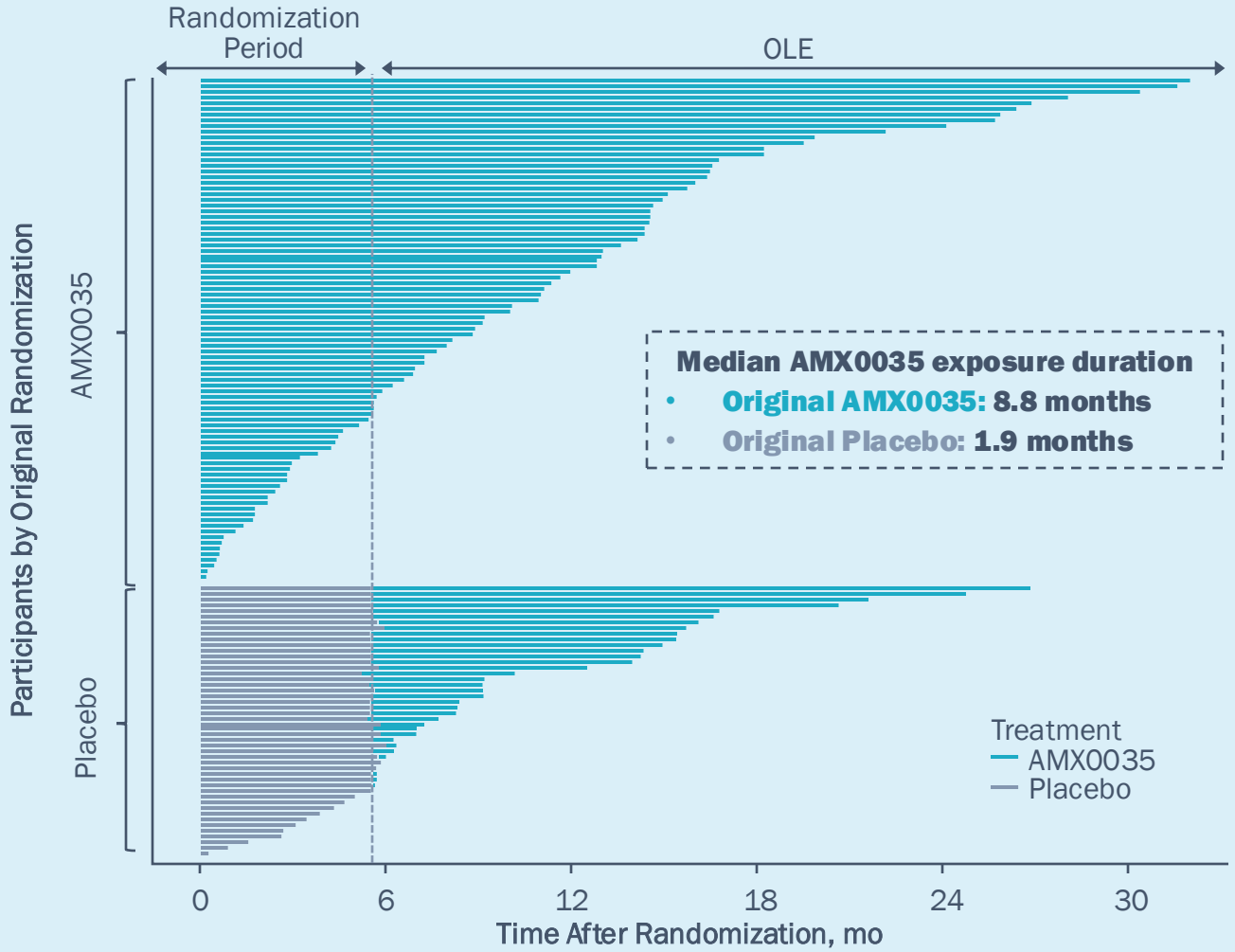
OLE, open-label extension.

Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091

AMX0035 Exposure Over Long-Term Follow-Up

- The majority (92%) of eligible participants from CENTAUR enrolled in the OLE
- It is important to note that most participants originally randomized to placebo received some exposure to AMX0035 in the OLE
  - The groups are referred to as **originally randomized to AMX0035** and **originally randomized to placebo** to highlight this point

Duration of AMX0035 Exposure for Each Randomized Participant

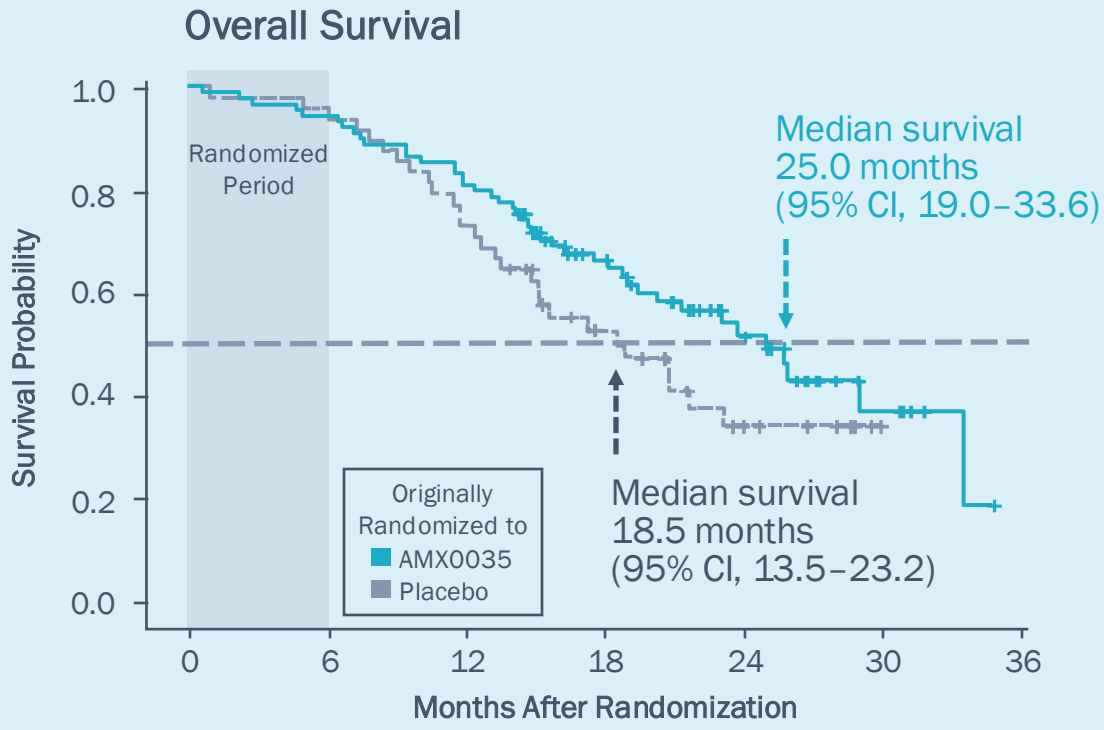


Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091

Risk of Death Was 44% Lower in the Group Originally Randomized to AMX0035

- Risk of death was 44% lower in the originally randomized to AMX0035 group; HR 0.56 (95% CI 0.34-0.92), ***P* = 0.023**
- 6.5 month longer median survival in the group originally randomized to AMX0035
- 77% of participants were on riluzole or edaravone at or prior to study entry

AMX0035 effect on survival was consistent regardless of baseline use of concomitant medications



Originally Randomized to:							
AMX0035	89	84	72	45	21	6	0
Placebo	48	46	35	19	9	0	0
No. Censored	0	0	0	15	31	42	47
	0	0	0	7	11	20	20
No. of Events	0	5	17	29	37	41	42
	0	2	13	22	28	28	28

Median survival is the time at which 50% of participants have died.

Paganoni S, et al. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27091

Key Study Events Over Long-Term Follow-Up

Methods

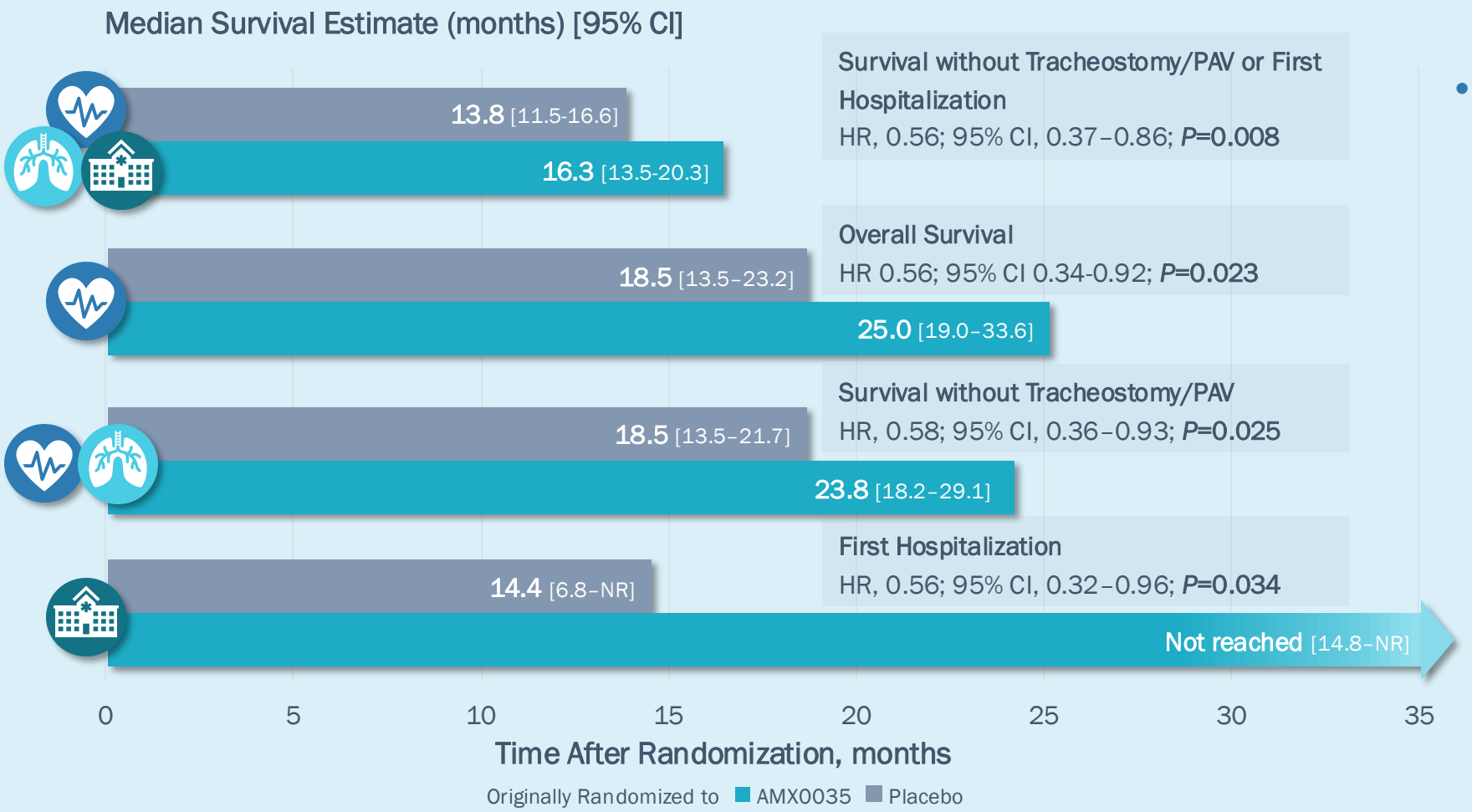
Survival	Tracheostomy/Permanent Assisted Ventilation (PAV) [>22 hours/day for >7 days]	First Hospitalization
• Captured via a search of public records for all participants* including those who discontinued, were lost to follow-up, or did not enroll in the OLE	• Recorded prospectively via clinic reports, with censoring at last date of follow-up for those without reported events • Shorter duration of observation than time to death	

- Events observed through July 2020; longest post-randomization follow-up, 35 months
- Hazard ratios (HRs) estimated using a Cox proportional hazards model with covariates of pre-baseline ALSFRS-R slope, baseline ALSFRS-R, and age

Data on File. Amylyx Pharmaceuticals.

*2 participants that could not be confirmed as of July 2020 were censored at the date of last contact with their clinical site.

Long-Term Risk of Death, Tracheostomy/PAV and Risk of First Hospitalization



- Long-term risk of death or tracheostomy/permanent assisted ventilation and risk of first hospitalization was significantly lower among participants originally randomized to AMX0035 versus placebo
  - Median difference in AMX0035 exposure between groups was 6.9 months

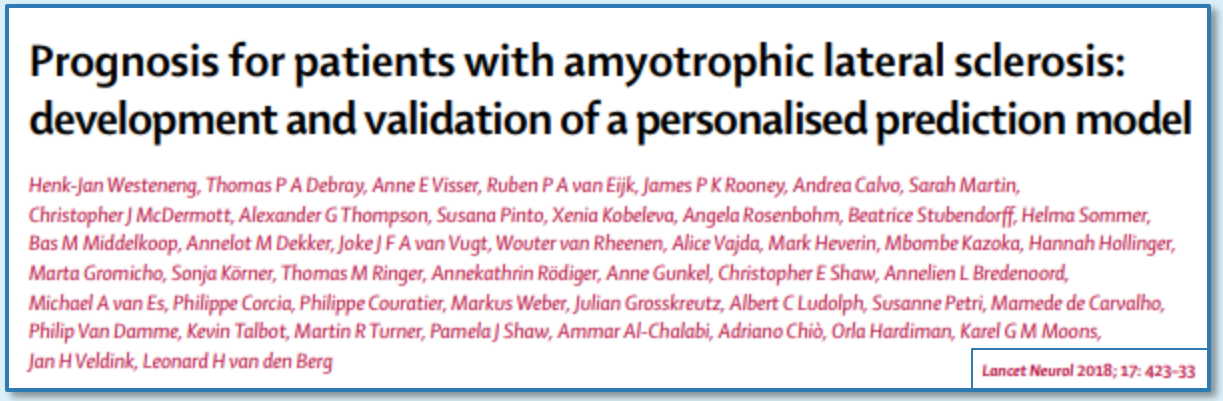
Kaplan Meier survival estimates. Time to death observation was longer than time to tracheostomy, PAV, and hospitalization. Potential for missing data after dropout for hospitalizations and ventilation/tracheostomy events.
Data on File. Amylyx Pharmaceuticals.

Comparing Observed to Predicted Survival

Novel Approaches

Challenge	Solution
The CENTAUR trial was designed to detect a significant difference in disease progression (ALSFRS-R) between AMX0035 and placebo groups in the shortest time possible – Even in a rapidly progressing ALS population, six months was not enough to detect a difference in survival	Assess long-term survival in ALL participants using a participant locating service
In the overall survival analysis, the placebo group is lost after 6 months as most participants entered the OLE and received AMX0035	Use the ENCALS survival prediction model to generate predicted survival for each group and then compare to actual survival

Exploratory Analysis: ENCALS Survival Prediction Model



Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model

Henk-Jan Westeneng, Thomas P A Debray, Anne E Visser, Ruben P A van Eijk, James P K Rooney, Andrea Calvo, Sarah Martin, Christopher J McDermott, Alexander G Thompson, Susana Pinto, Xenia Kobeleva, Angela Rosenbohm, Beatrice Stubendorff, Helma Sommer, Bas M Middelkoop, Annelot M Dekker, Joke J F A van Vugt, Wouter van Rheenen, Alice Vajda, Mark Heverin, Mbombe Kazoka, Hannah Hollinger, Marta Gromicho, Sonja Körner, Thomas M Ringer, Annekathrin Rödiger, Anne Gunkel, Christopher E Shaw, Annelien L Bredenoord, Michael A van Es, Philippe Corcia, Philippe Couratier, Markus Weber, Julian Grosskreutz, Albert C Ludolph, Susanne Petri, Mamede de Carvalho, Philip Van Damme, Kevin Talbot, Martin R Turner, Pamela J Shaw, Ammar Al-Chalabi, Adriano Chiò, Orla Hardiman, Karel G M Moons, Jan H Veldink, Leonard H van den Berg

Lancet Neurol 2018; 17: 423–33

- The model produced individual survival predictions for the participants in CENTAUR
- These predictions were used to compare actual survival in CENTAUR vs. predicted survival
  - Time to median survival probability was used to derive predicted survival

Predictors Included in Model

- Age at onset
- Forced vital capacity
- Diagnostic delay
- ALSFRS-R slope
- Bulbar onset
- Definite ALS, revised El Escorial criteria
- Presence of frontotemporal dementia*
- Presence of a *C9orf72* repeat expansion*

Data courtesy of

TRICALS

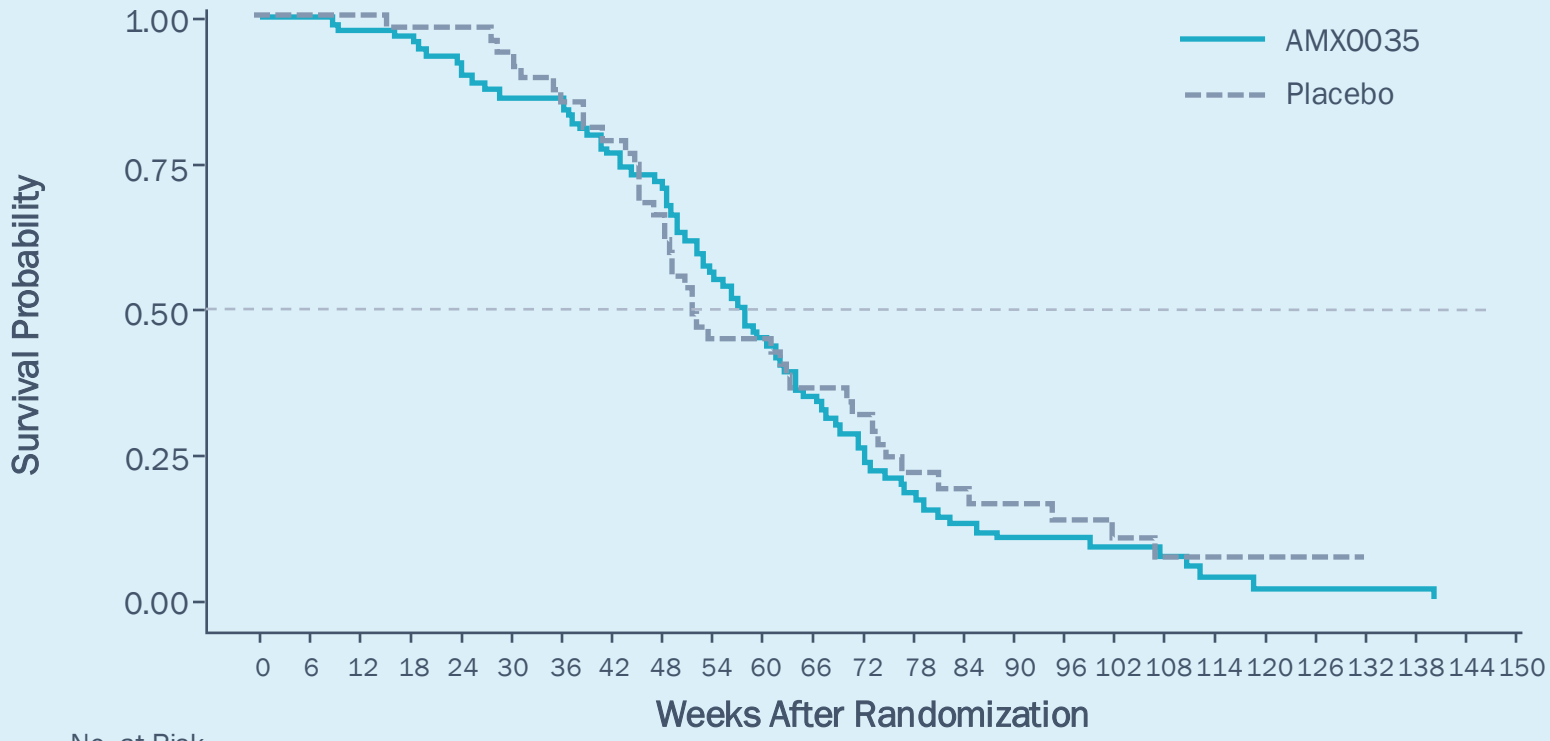
The highway towards a cure

*Variables were incomplete in CENTAUR population.
Westeneng HJ, et al. Lancet Neurol. 2018 May;17(5):423-433.

Original AMX0035 and Original Placebo Groups Had Similar Probability of Survival

- Predicted median survival durations from CENTAUR baseline were 13.5 months in the group originally randomized to AMX0035 and 12.0 months in the group originally randomized to placebo

Predicted Baseline Median Survival Probabilities in CENTAUR Participants By Originally Randomized Treatment



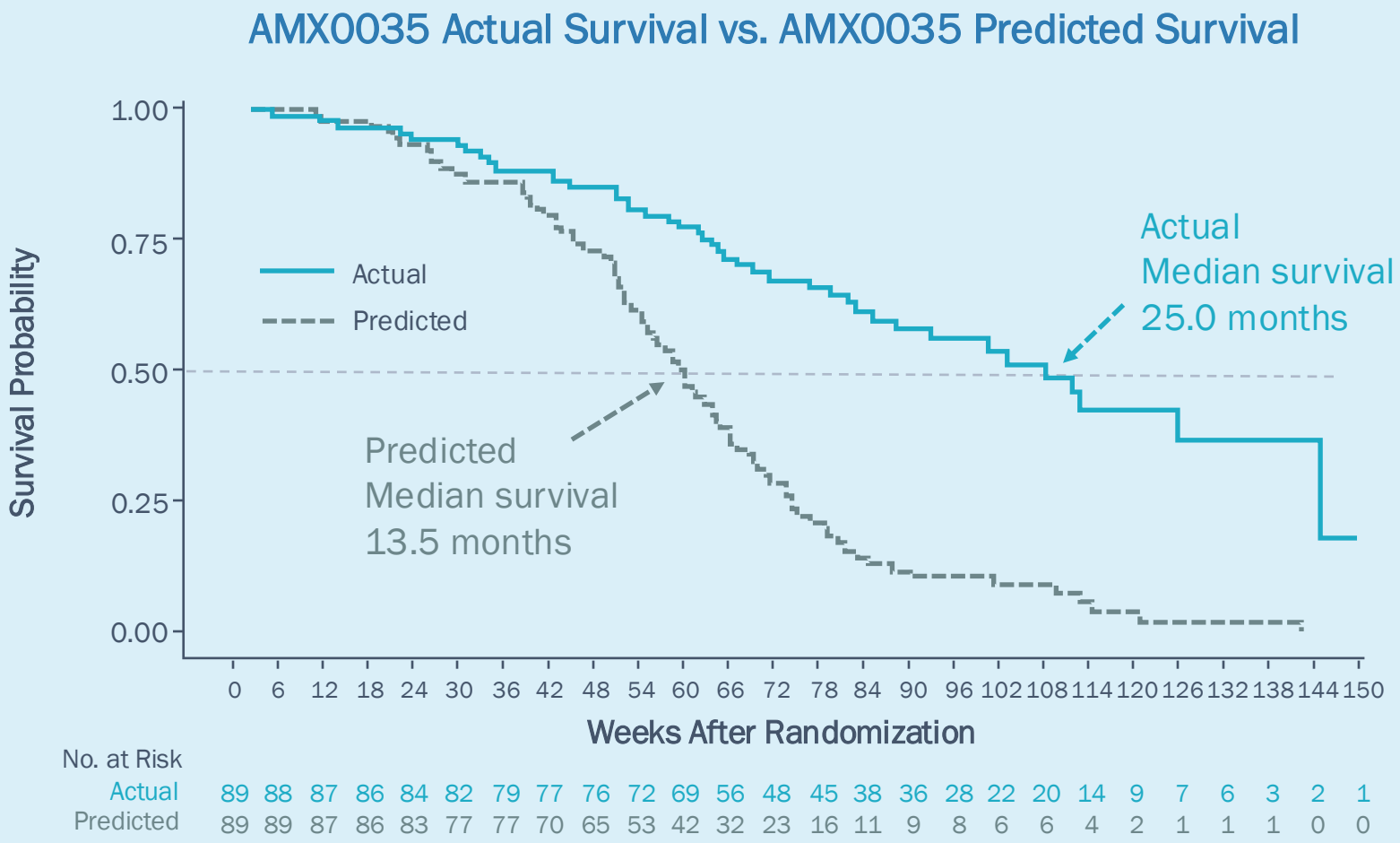
No. at Risk

AMX0035	89	89	87	86	83	77	77	70	65	53	42	32	23	16	11	9	8	6	6	4	2	1	1	1	0	0
Placebo	48	48	48	47	47	45	42	38	32	22	22	18	14	9	8	7	6	4	3	1	1	1	0	0	0	0

Data on File. Amylyx Pharmaceuticals.

Actual Survival was Longer Than Predicted in the Group Originally Randomized to AMX0035

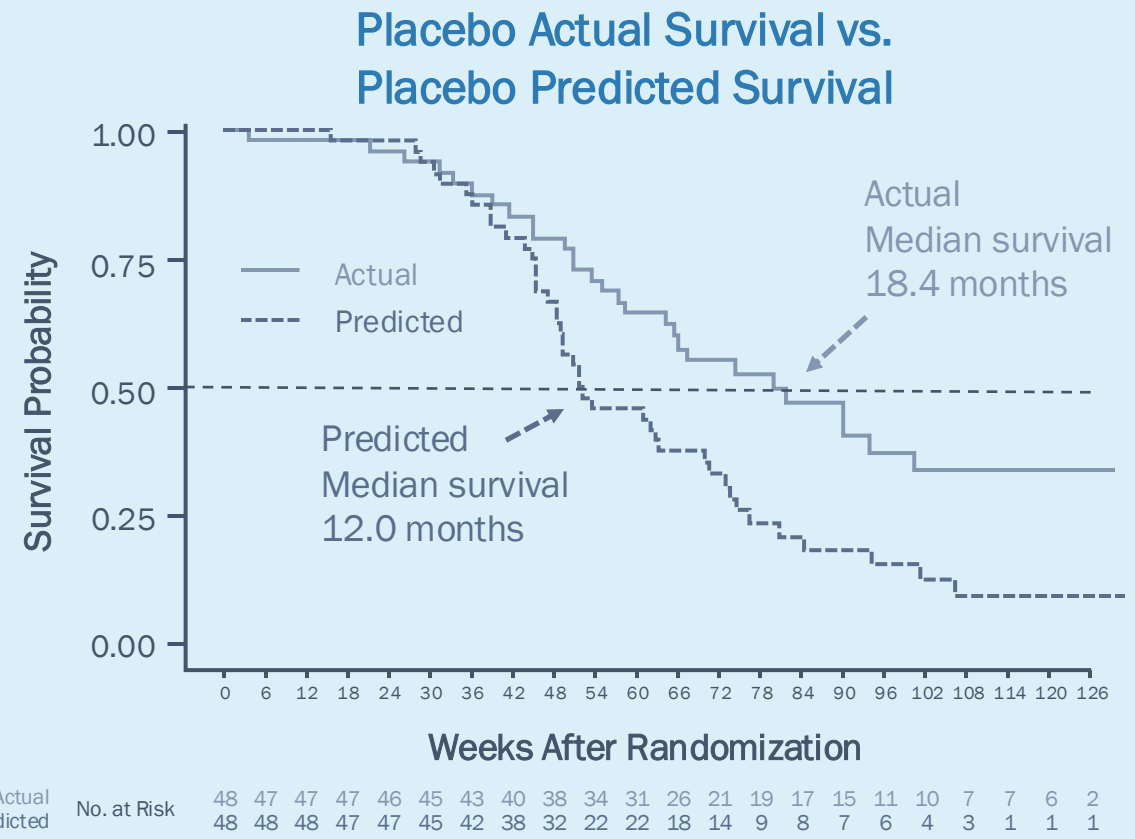
- 11.5 months longer median survival than predicted in originally randomized to AMX0035 group



Data on File. Amylyx Pharmaceuticals.

Actual Survival was Longer Than Predicted in the Group Originally Randomized to Placebo

- The majority of the originally randomized to placebo group received AMX0035 with a 24-week delayed start in the OLE
- 6.4 month longer median survival compared to predicted in the originally randomized to placebo group
- The group of placebo participants (n=14) that never received AMX0035 did not have a significant difference between actual and predicted survival



Data on File. Amylyx Pharmaceuticals.

Conclusions

Summary

- Administration of AMX0035 is associated with **both a statistically significant functional and survival benefit** in people with ALS[1-3]
  - Significant slowing of ALSFRS-R decline over the 6-month randomized period
  - 6.5 month longer median survival in the group originally randomized to AMX0035 in the pre-specified overall survival analysis
  - Exploratory analysis using the ENCALS survival prediction model raises the potential that participants in CENTAUR who received delayed exposure to AMX0035 may also have a survival benefit in addition to the originally randomized to AMX0035 group
- Similar rates of adverse events were recorded in the AMX0035 and placebo groups during the 24-week randomized period[2]

The novel approaches to gather and analyze survival data for all participants in CENTAUR may prove useful in future trials; allowing the collection of meaningful survival information despite a short randomized period

1. Paganoni S, et al. Muscle Nerve. 2020. https://doi.org/10.1002/mus.27091. **2.** Paganoni S, et al. NEJM. 2020;383:919-930. **3.** Data on File. Amylyx Pharmaceuticals.

Thank you!

CENTAUR participants and their families

- CENTAUR Study Group
- Merit Cudkowicz, MD, MSc
- Leonard van den Berg, MD, PhD, Henk-Jan Westeneng, MD, and Ruben van Eijk, MD, PhD

Individuals have provided consent to use their images on this slide.