USE OF SUPPLEMENTAL DATA FOR REGULATORY DECISION-MAKING IN ALS

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Disclosures

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ALS is a fatal and rapidly progressing disease

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

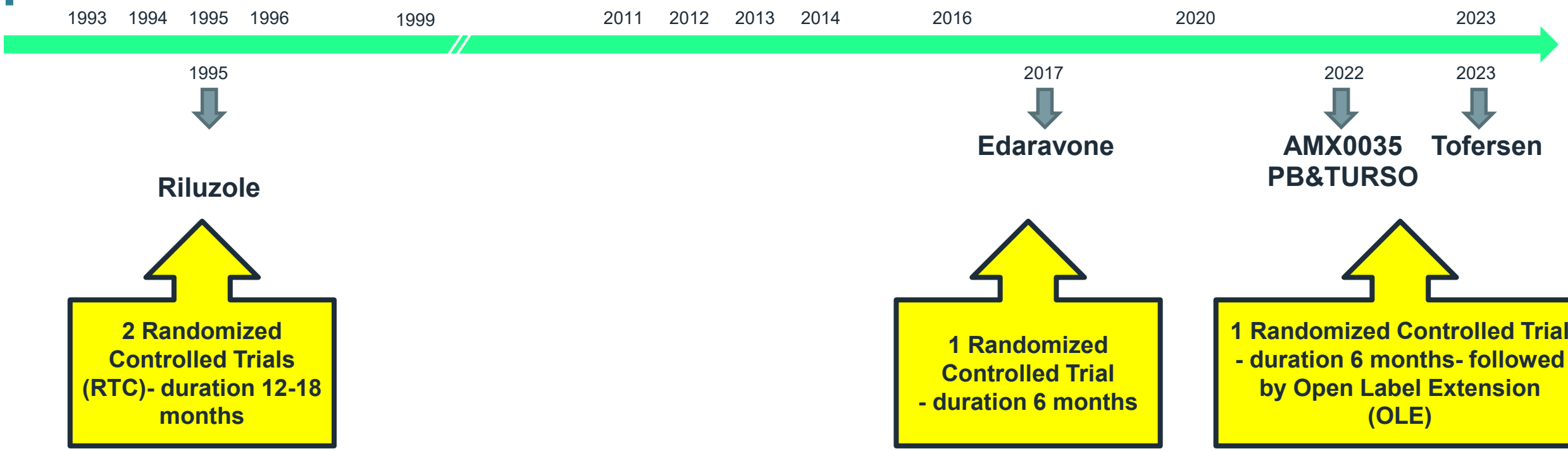
Accelerating innovation

Merit Cudkowicz, MD, MSc
Sean M. Healey

"Work with a sense of urgency, as if your life depended on it"

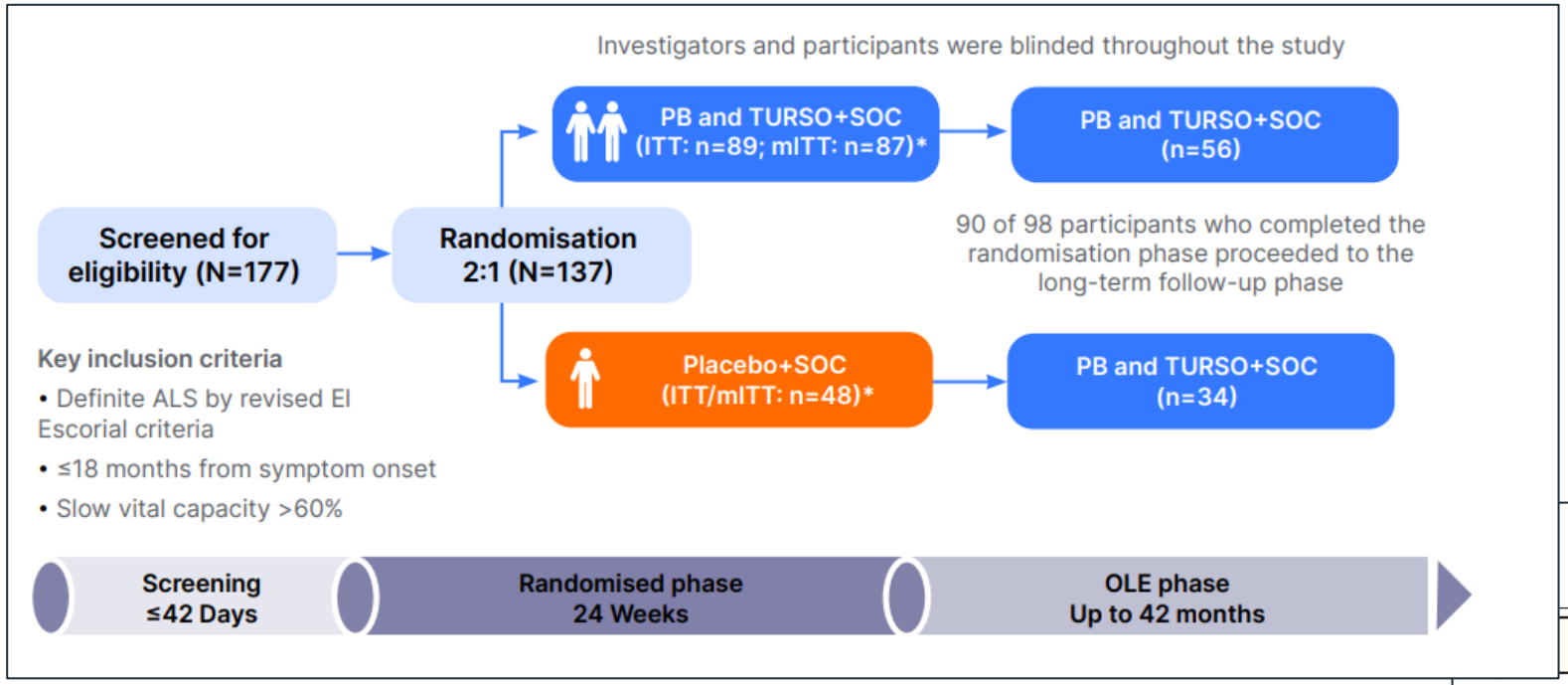
Sandy Morris

ALS Trial Design Has Evolved



Approval of AMX0035 (PB&TURSO)

AMX0035 (PB&TURSO) TRIAL SCHEMA



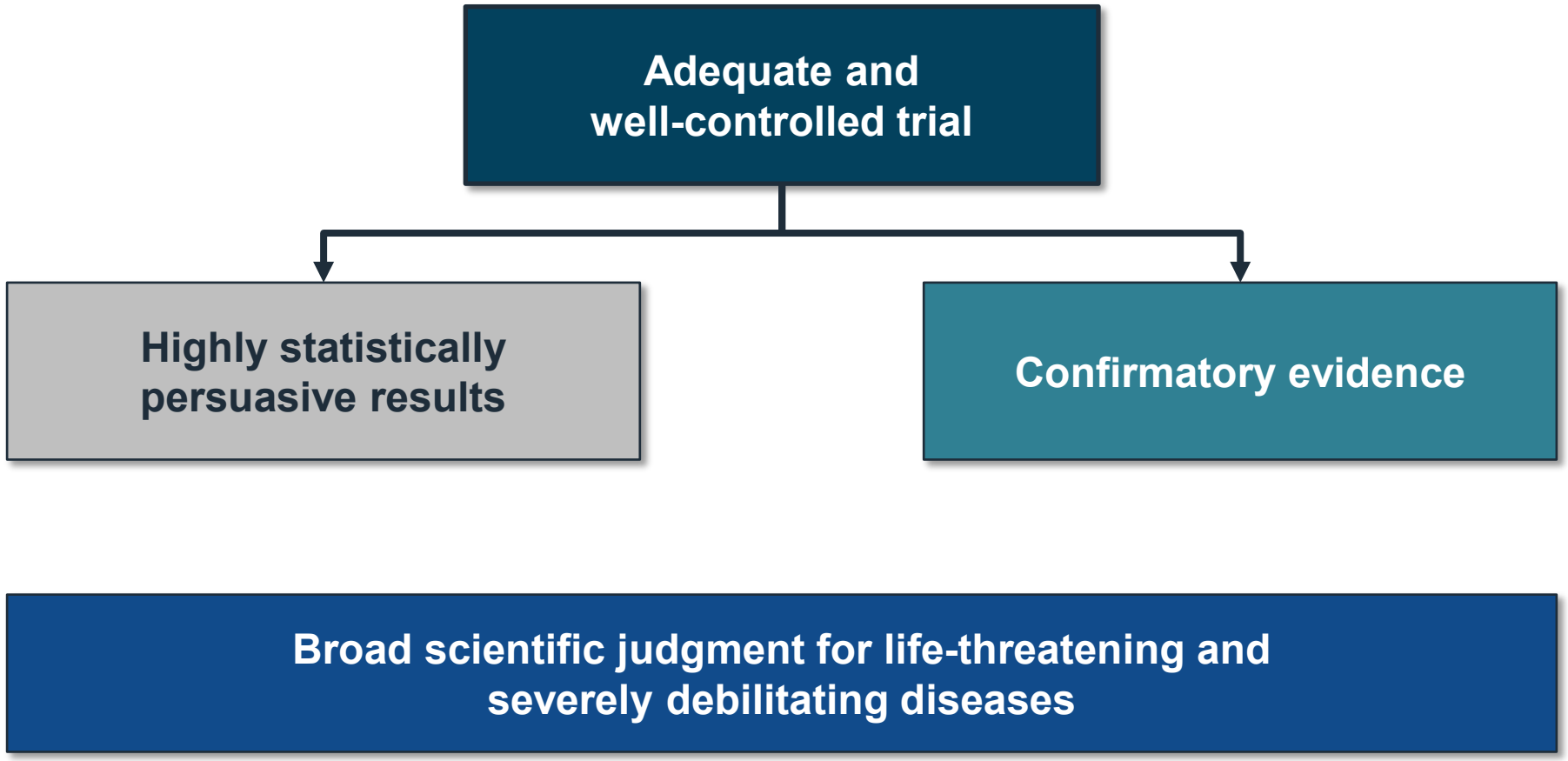
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis

S. Paganoni, E.A. Macklin, S. Hendrix, J.D. Berry, M.A. Elliott, S. Maiser, C. Karam, J.B. Caress, M.A. Owegi, A. Quick, J. Wymer, S.A. Goutman, D. Heitzman, T. Heiman-Patterson, C.E. Jackson, C. Quinn, J.D. Rothstein, E.J. Kasarskis, J. Katz, L. Jenkins, S. Ladha, T.M. Miller, S.N. Scelsa, T.H. Vu, C.N. Fournier, J.D. Glass, K.M. Johnson, A. Swenson, N.A. Goyal, G.L. Pattee, P.L. Andres, S. Babu, M. Chase, D. Dagostino, S.P. Dickson, N. Ellison, M. Hall, K. Hendrix, G. Kittle, M. McGovern, J. Ostrow, L. Pothier, R. Randall, J.M. Shefner, A.V. Sherman, E. Tustison, P. Vigneswaran, J. Walker, H. Yu, J. Chan, J. Wittes, J. Cohen, J. Klee, K. Leslie, R.E. Tanzi, W. Gilbert, P.D. Yeramian, D. Schoenfeld, and M.E. Cudkowicz

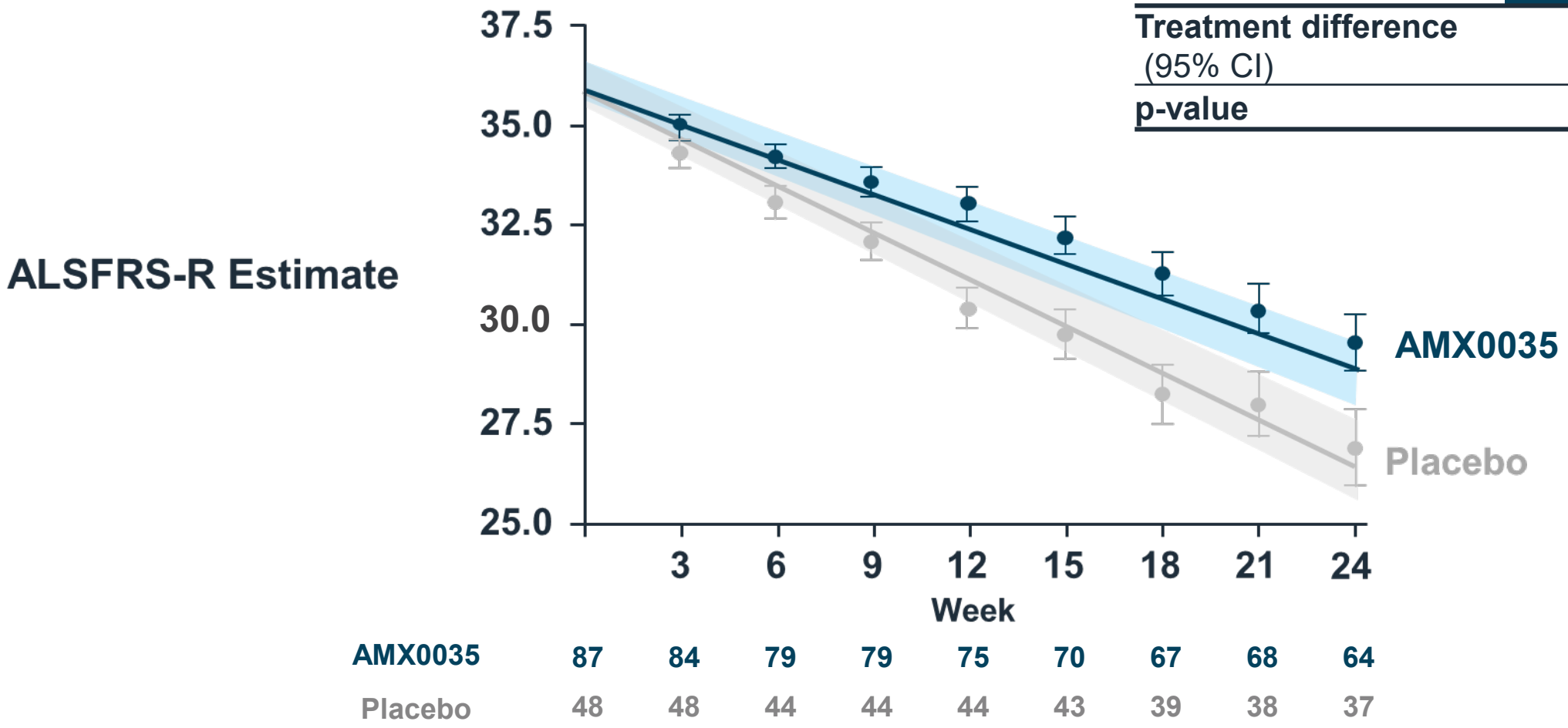
Two Options for Meeting Substantial Evidence of Efficacy Based on Single Trial



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

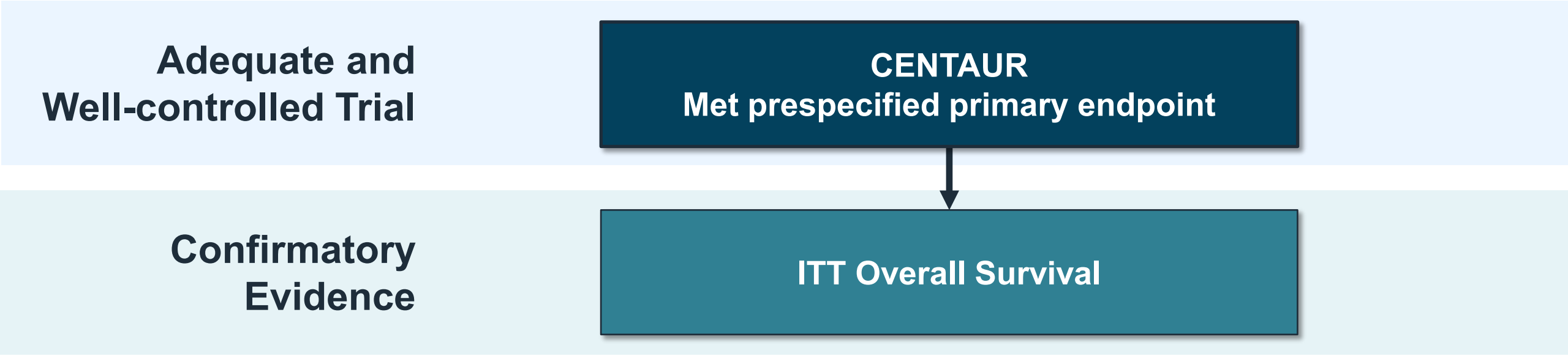
AMX0035 Leads to 2.32 Point Treatment Difference at Week 24

	AMX0035 + SOC (N = 87)	Placebo + SOC (N = 48)
Treatment difference (95% CI)	**2.32 points** (0.18, 4.47)	
p-value	**0.034**	



mITT population

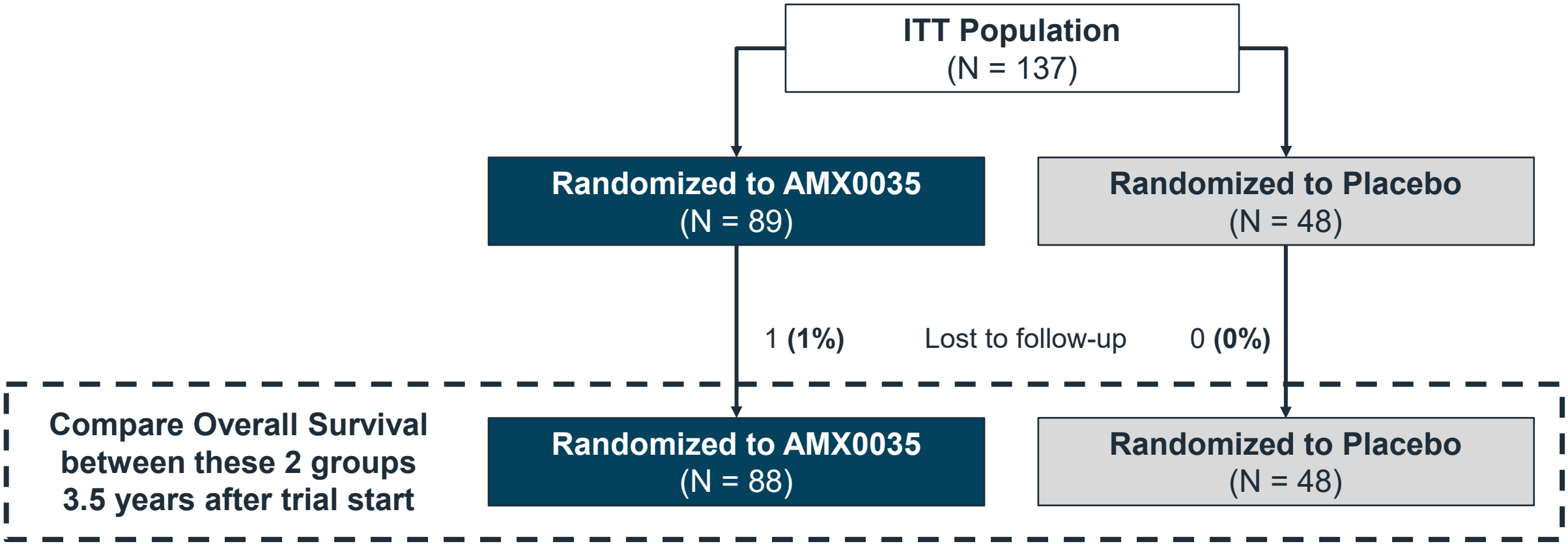
ITT Overall Survival As Confirmatory Evidence



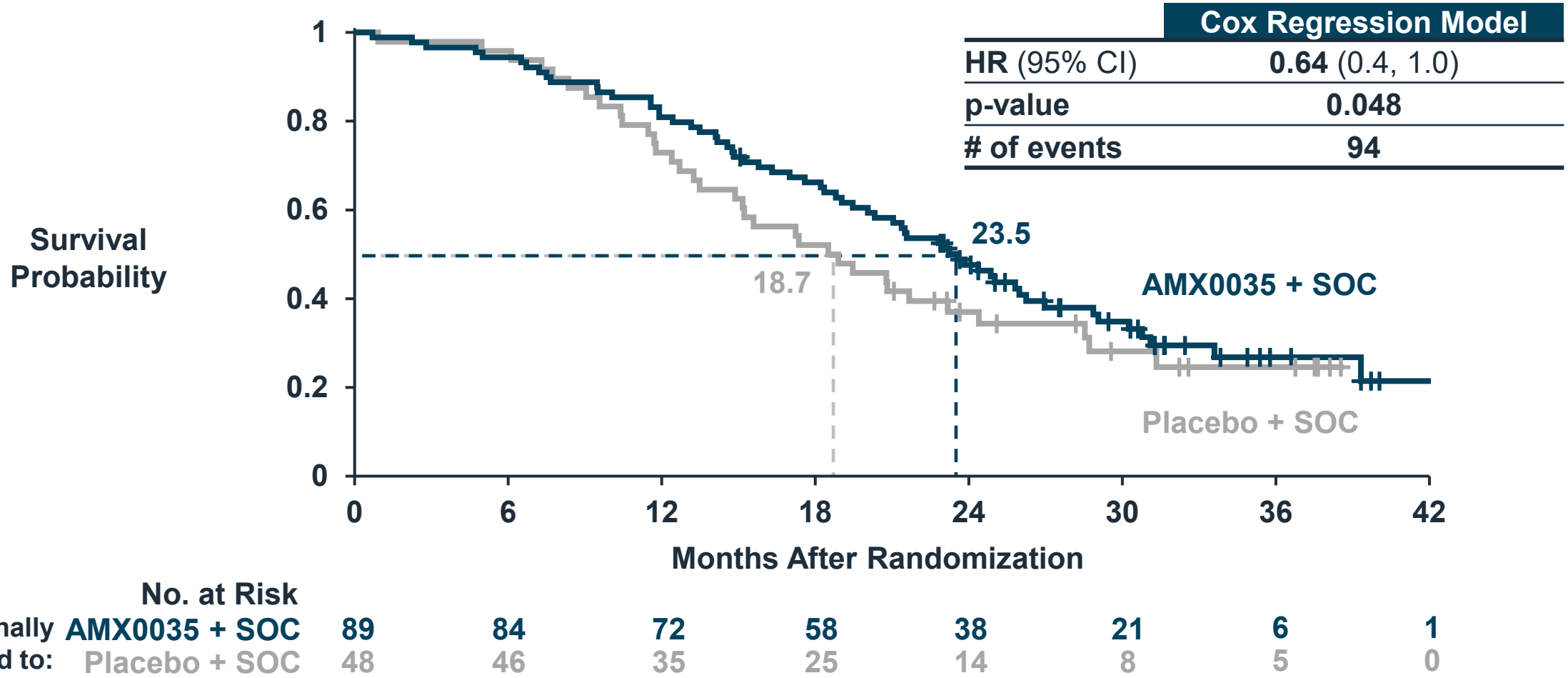
- **2017 FDA Guidance:** *"For many serious diseases, there is an endpoint of such great clinical importance that it is unreasonable not to collect and analyze the endpoint data; the usual example is **mortality**..."*

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

ITT Overall Survival Analysis – Randomized, Blinded, Long-Term, and Complete Data



AMX0035 Overall Survival Benefit in ITT Population



Post hoc analysis

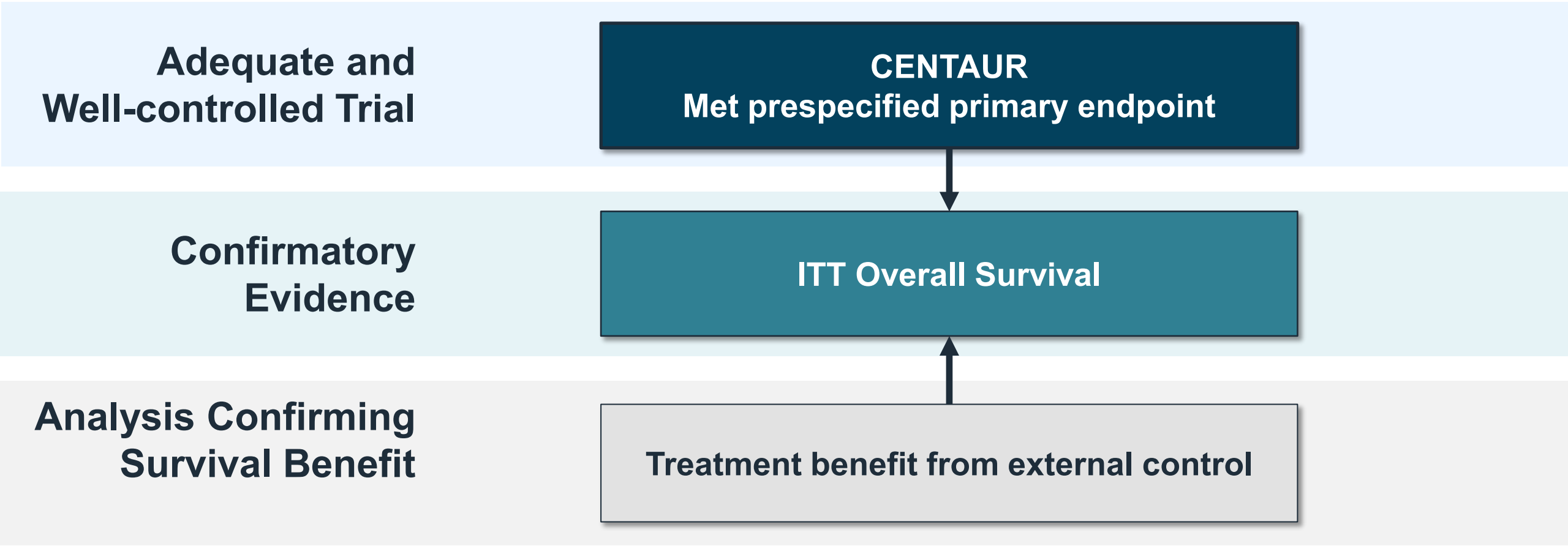
FDA Guidance Allows for Use of Concurrent or External Controls to Confirm Benefit

- ITT Overall Survival used conservative analysis

> 3. *One adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of the disease*
>
> In certain circumstances, FDA accepts one adequate and well-controlled clinical investigation that has generated compelling results as the basis to demonstrate effectiveness, when the single trial is supported by additional data from the natural history of the disease that reinforce the very persuasive finding. 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.

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

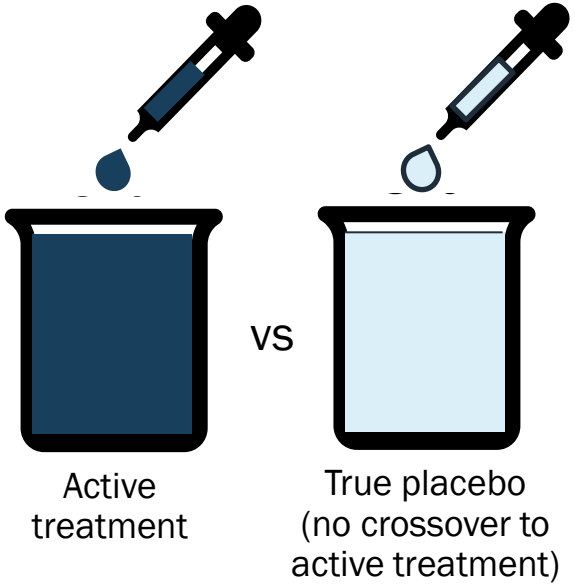
External Control Analysis Supports ITT OS Benefit



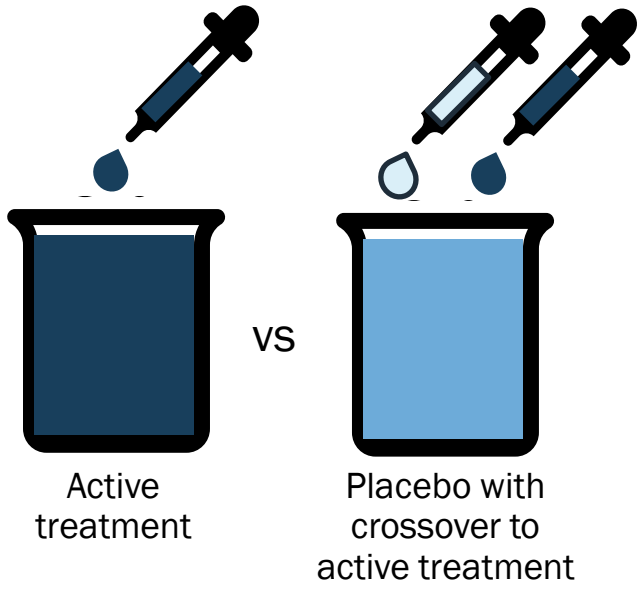
Rationale For Performing the PRO-ACT Survival Analysis

Effect of Crossover Design in Clinical Trials

Trial without treatment crossover



Trial with treatment crossover



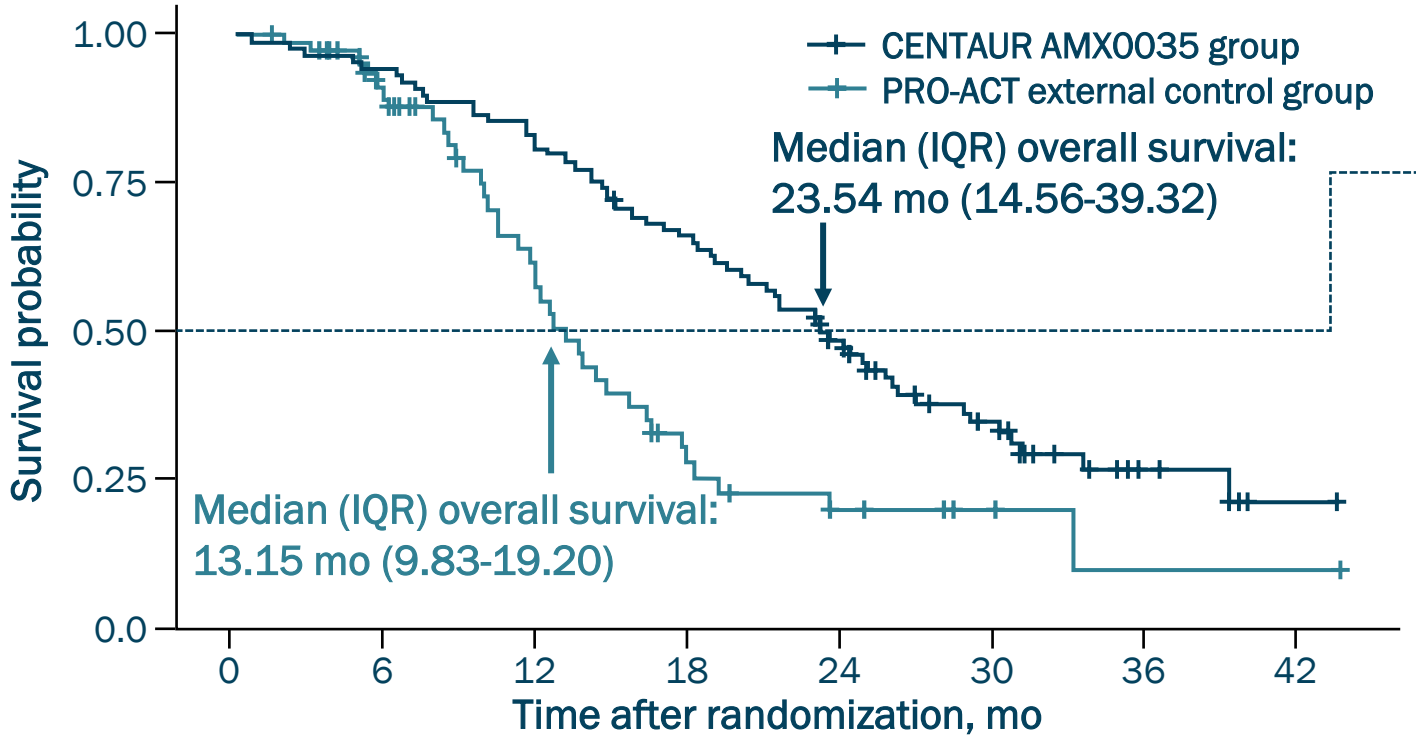
CENTAUR OLE

- **71%** of participants originally randomized to placebo crossed over to active treatment after 6 months
- Placebo-to-active crossover may lead to underestimation of the effect of investigational therapies on overall survival

In this analysis, a treatment-naïve external control comparator arm was used to estimate the treatment effect of AMX0035 on survival in the absence of placebo-to-active crossover

1. Ishak KJ, et al. *Pharmacoeconomics*. 2014;32(6):533-546. **2.** Jönsson L, et al. *Value Health*. 2014;17(6):707-713. **3.** Paganoni S, et al. *Ann Clin Transl Neurol*. Published online October 9, 2023. doi:10.1002/acn3.51915.

Survival in CENTAUR AMX0035 Arm vs PRO-ACT External Control Arm



Median overall survival was 10.39 months longer in the CENTAUR AMX0035 group vs the PRO-ACT external control group

Risk of death was 52% lower in the CENTAUR AMX0035 group vs the PRO-ACT external control group (HR, 0.48; 95% CI, 0.31-0.72; P=.00048)

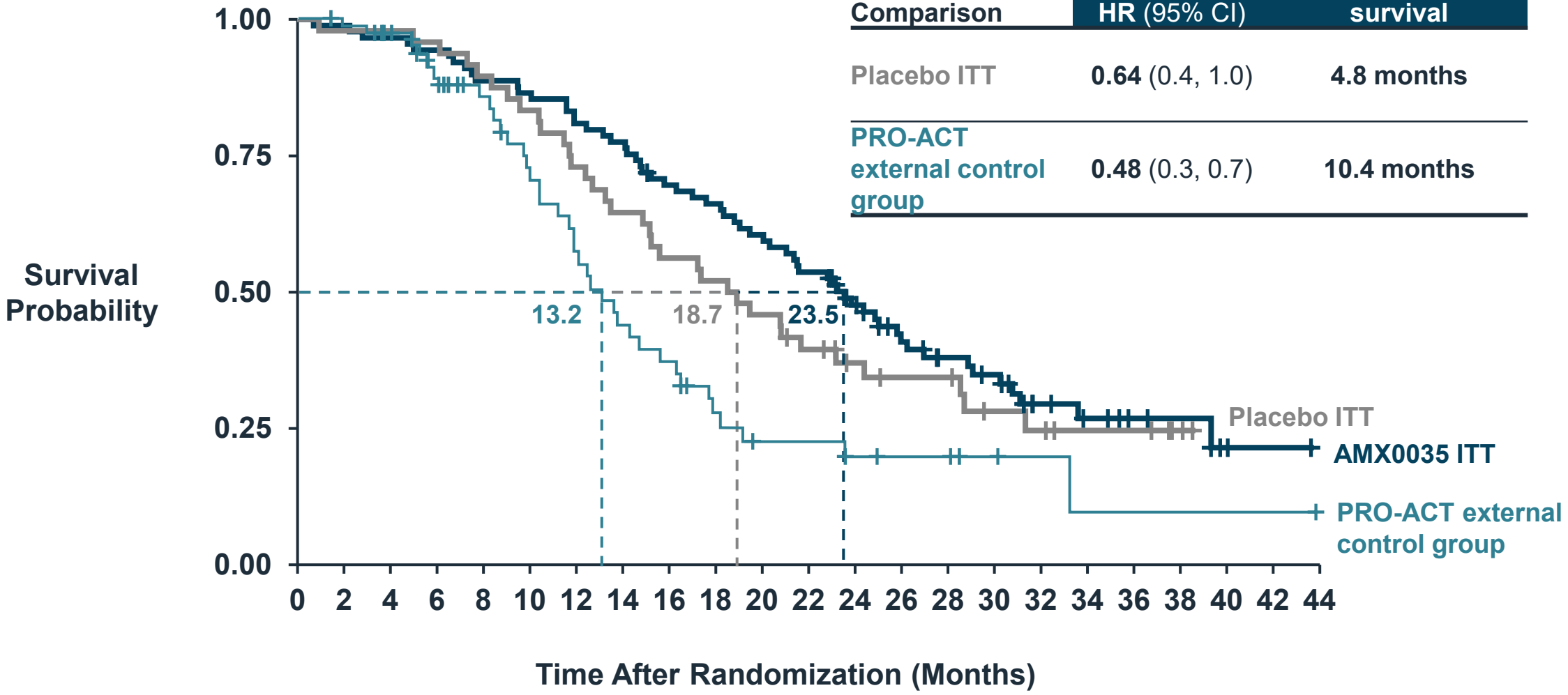
Number at risk

CENTAUR AMX0035 group	89	84	72	58	38	21	6	1
PRO-ACT external control group	85	62	27	11	6	3	1	1

Paganoni S, et al. *Ann Clin Transl Neurol*. Published online October 9, 2023. doi:10.1002/acn3.51915.

Survival Comparison: Original Placebo Group (with Crossover) vs. PRO-ACT External Control Arm

AMX0035 ITT Comparison	HR (95% CI)	Difference median survival
Placebo ITT	**0.64** (0.4, 1.0)	**4.8 months**
PRO-ACT external control group	**0.48** (0.3, 0.7)	**10.4 months**



Approval of tofersen

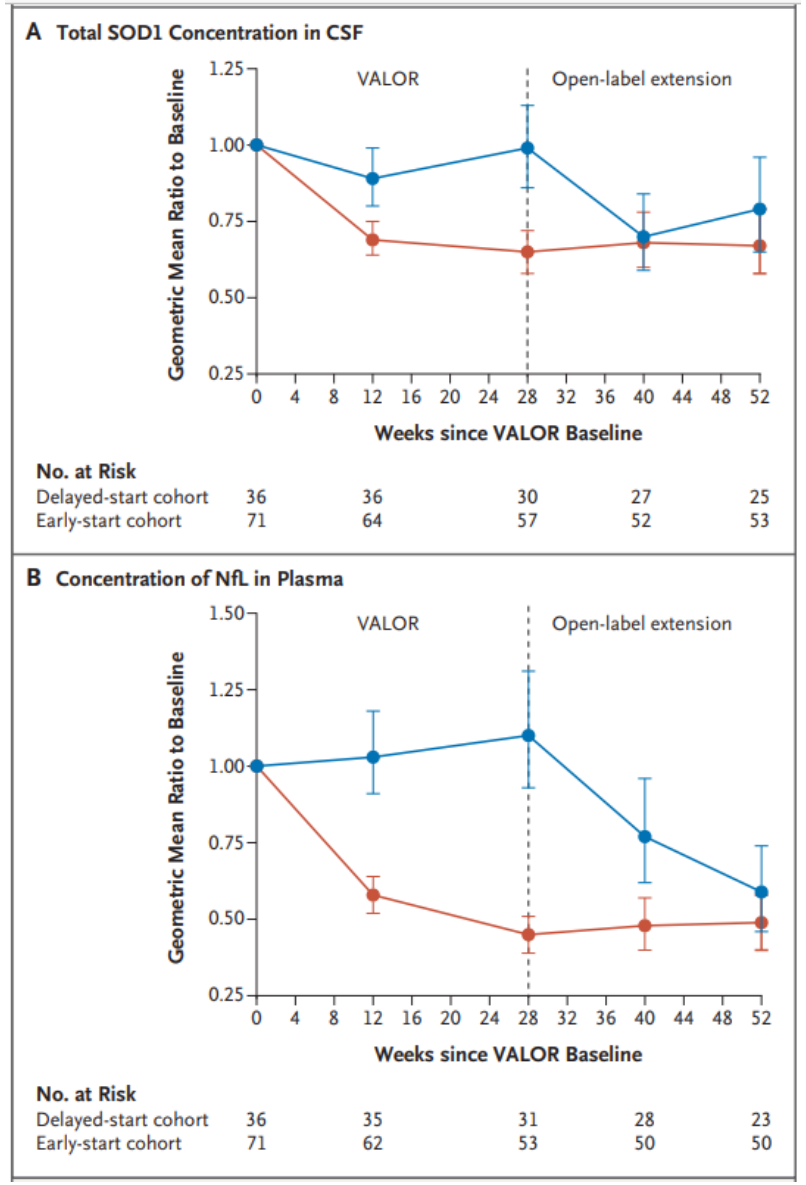
Tofersen: accelerated approval for SOD1 ALS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T.M. Miller, M.E. Cudkowicz, A. Genge, P.J. Shaw, G. Sobue, R.C. Bucelli, A. Chiò, P. Van Damme, A.C. Ludolph, J.D. Glass, J.A. Andrews, S. Babu, M. Benatar, C.J. McDermott, T. Cochrane, S. Chary, S. Chew, H. Zhu, F. Wu, I. Nestorov, D. Graham, P. Sun, M. McNeill, L. Fanning, T.A. Ferguson, and S. Fradette, for the VALOR and OLE Working Group*

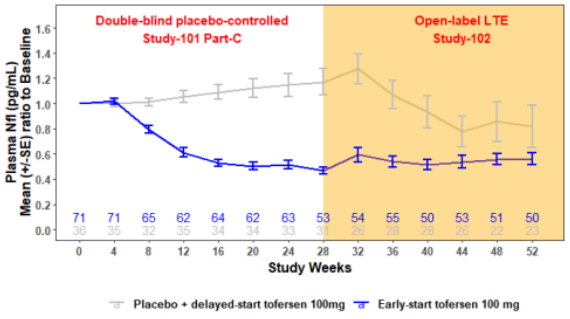


Tofersen: accelerated approval for SOD1 ALS

Longitudinal Changes in Plasma NfL and ALSFRS-R in Study Completers

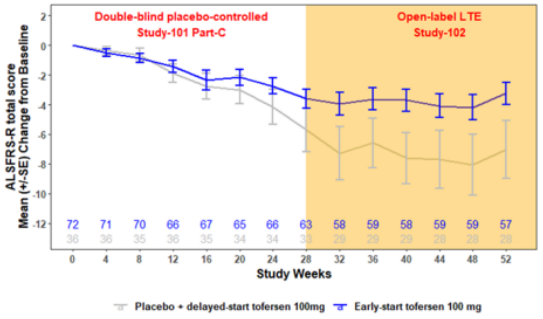
- Early-start and delayed-start group showed similar NfL reduction upon initiation of tofersen treatment

Plasma NfL



- Early-start group had consistently less numerical decline in ALSFRS-R total scores as compared to delayed-start group

ALSFRS-R total score



Conclusion

- Tofersen treatment led to a reduction in total CSF SOD1 protein and plasma NfL in SOD1-ALS patients
- Plasma NfL appears to be a reasonably likely surrogate endpoint for SOD1-ALS based on the following:
  - Mechanistic support based on SOD1-ALS pathophysiology and the pharmacology of tofersen
  - Demonstration of the prognostic value of plasma NfL in ALS
  - Relationship between plasma NfL reduction and ALSFRS-R total score
- In long-term treatment study, early-start tofersen group showed a less decline in ALSFRS-R total scores from Week 8 onwards as compared to delayed-start group, which support the potential treatment effect of tofersen

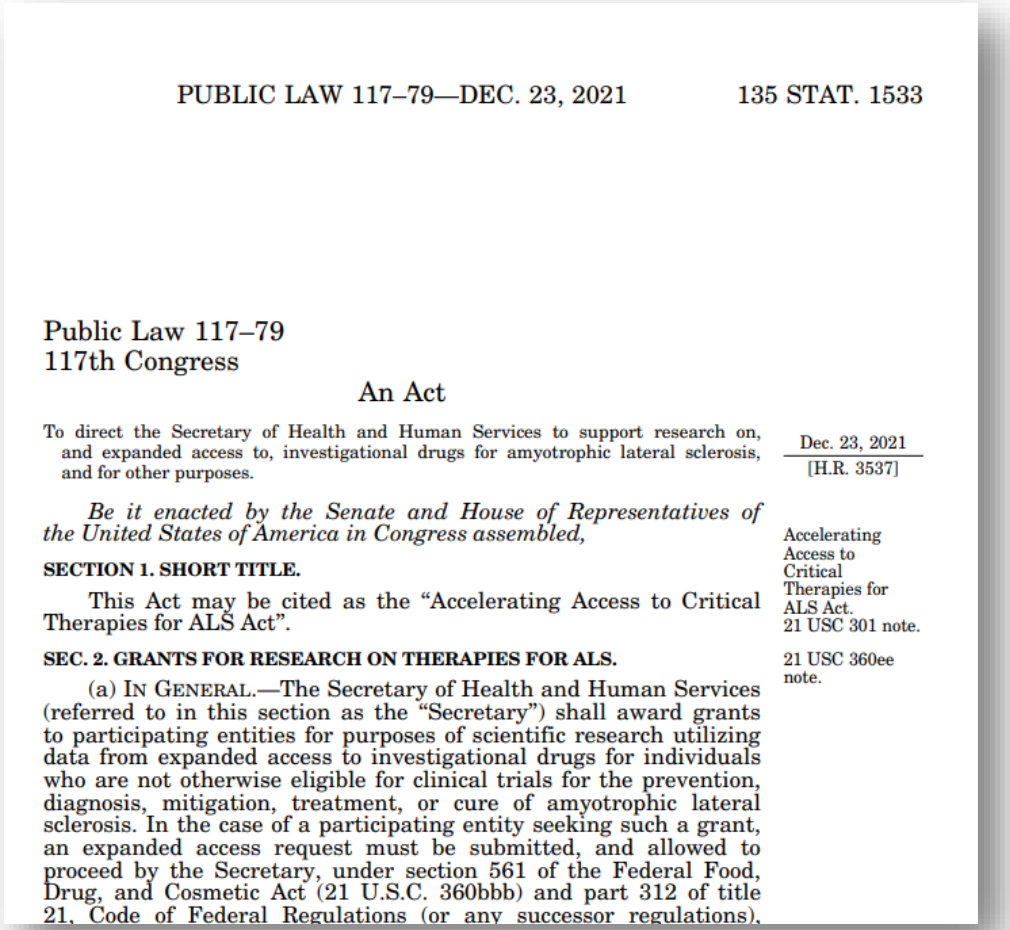
Expanded Access Protocol (EAPs)

ACT for ALS–A New Opportunity to Expand Access and Collect Supplemental Data in Parallel to Clinical Trials

Signed into law on December 23, 2021[1]

Grants for Research on Therapies via Intermediate-Size EAPs [1,2]

- NIH U01 grant mechanism[2]
- EAP must run in parallel to efficacy trial
- 2022: MGH Healey Center received the first EAP[2,3]
- 2023: MGH receives 2 additional EAP grants



PUBLIC LAW 117–79—DEC. 23, 2021 135 STAT. 1533

Public Law 117–79
117th Congress

An Act

To direct the Secretary of Health and Human Services to support research on, and expanded access to, investigational drugs for amyotrophic lateral sclerosis, and for other purposes.

Dec. 23, 2021
[H.R. 3537]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Accelerating Access to Critical Therapies for ALS Act.
21 USC 301 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Accelerating Access to Critical Therapies for ALS Act".

21 USC 360ee note.

SEC. 2. GRANTS FOR RESEARCH ON THERAPIES FOR ALS.

(a) IN GENERAL.—The Secretary of Health and Human Services (referred to in this section as the "Secretary") shall award grants to participating entities for purposes of scientific research utilizing data from expanded access to investigational drugs for individuals who are not otherwise eligible for clinical trials for the prevention, diagnosis, mitigation, treatment, or cure of amyotrophic lateral sclerosis. In the case of a participating entity seeking such a grant, an expanded access request must be submitted, and allowed to proceed by the Secretary, under section 561 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb) and part 312 of title 21, Code of Federal Regulations (or any successor regulations),

NIH, National Institute of Health.
1. Pub L No. 117-7+, 135 Stat 1533. **2.** News release. Sean M. Healy & AMG Center for ALS at Mass General; September 30, 2022. Accessed November 2, 2023. https://www.massgeneral.org/neurology/als/news/healeyamg-awarded-ninds-uo1-grant. **3.** HEALEY ALS Platform Trial Regimen E. Accessed November 8, 2023. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.massgeneral.org/assets/mgh/pdf/neurology/als/platform_trial_regimen_e_brochure.pdf

Conclusions

- “Supplemental data” has been used in regulatory-decision making in ALS
- Sources of data include Open Label Extension (OLEs) studies and comparison to external controls
- Expanded Access may provide an additional source of supplemental data