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

Merit Cudkowicz, MD
Director, Healey Center for ALS at Mass General

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

MASSACHUSETTS GENERAL HOSPITAL

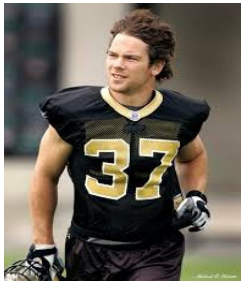
HARVARD MEDICAL SCHOOL

ALS THERAPIES NEW HOPE AND OPTIONS

NORTHEAST ALS CONSORTIUM JUNE 7TH, 2021

Disclosures: Consulting -Takeda, Cytokinetics, Immunity Pharm, Sunovian, Biogen, Avexis, Wave, Orion

Amyotrophic lateral sclerosis
Rapidly increasing globally



Lifetime risk 1:300 men, 1:400 woman

20-90 years of age (55); 10% familial

>160 pharma companies

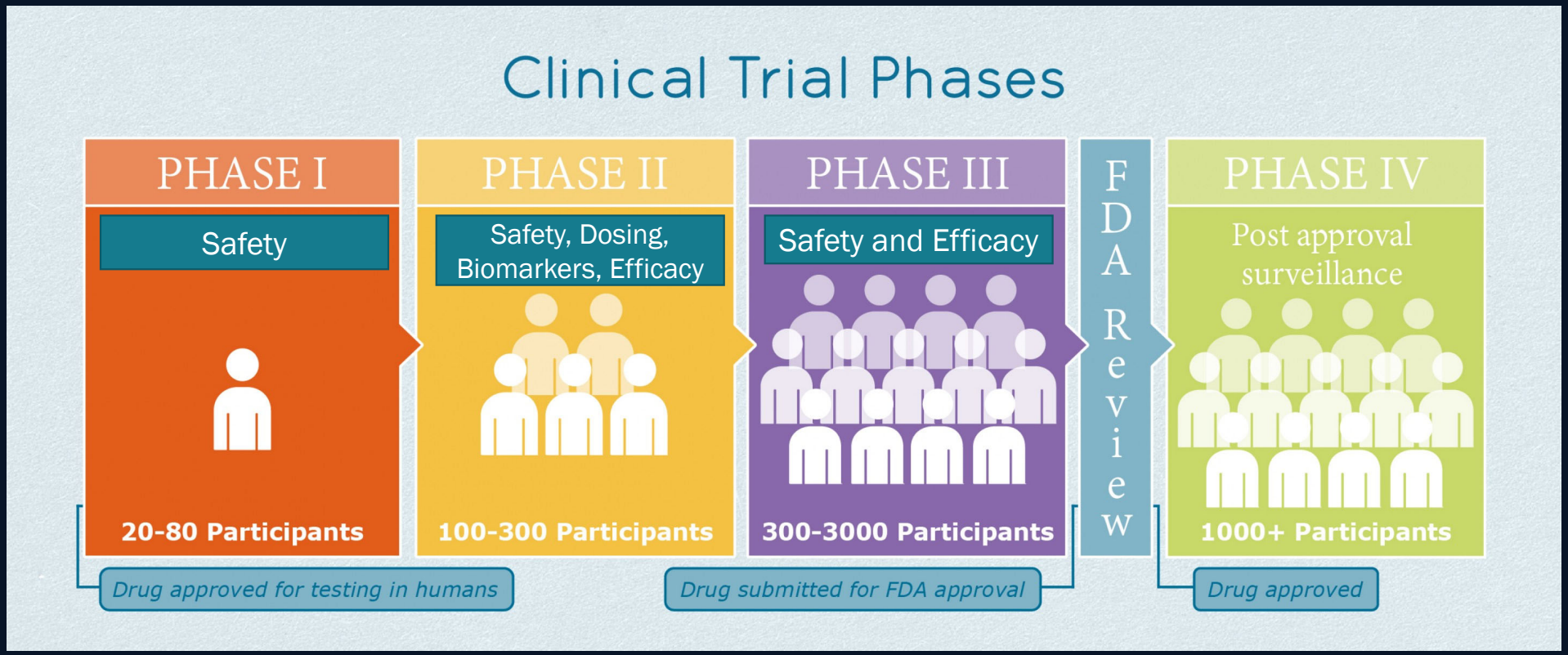
Powerful & Effective Activist Community – speed and options

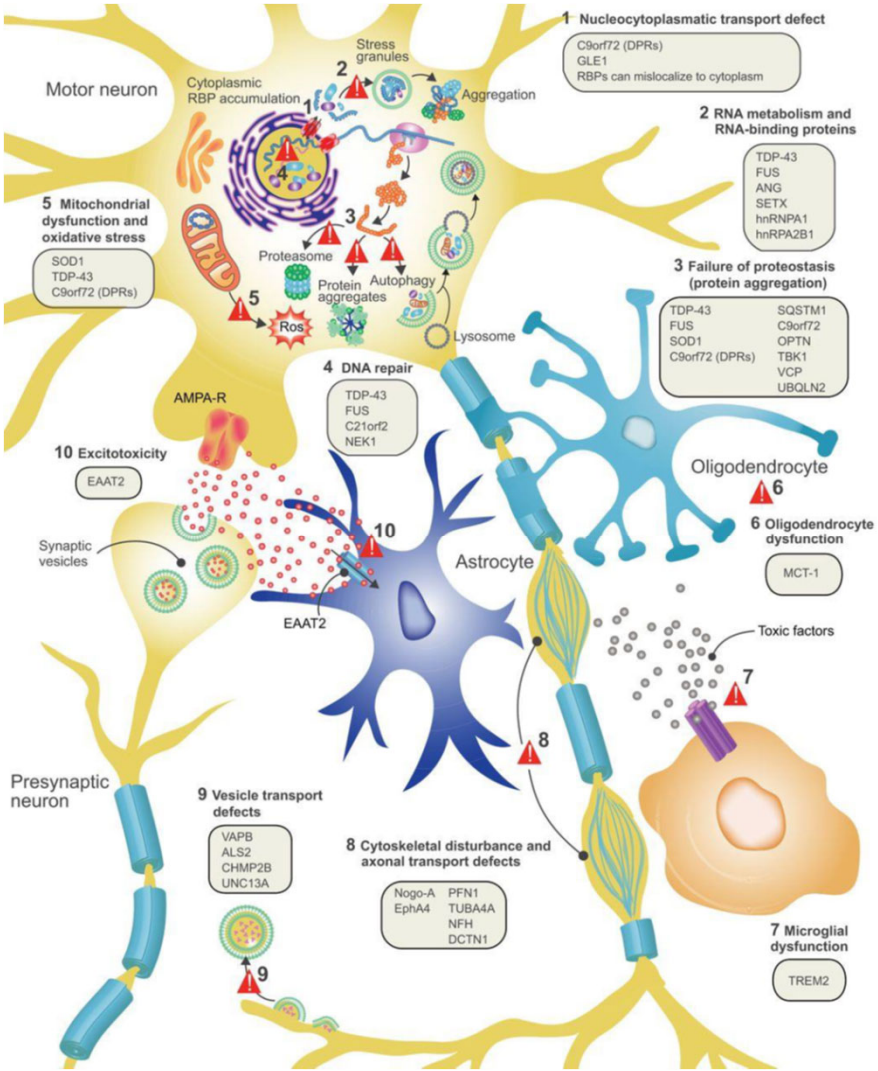
Therapies in Late Stage Testing

Therapeutic pipeline

HEALEY ALS Platform Trial

A typical drug development program includes 3 phases

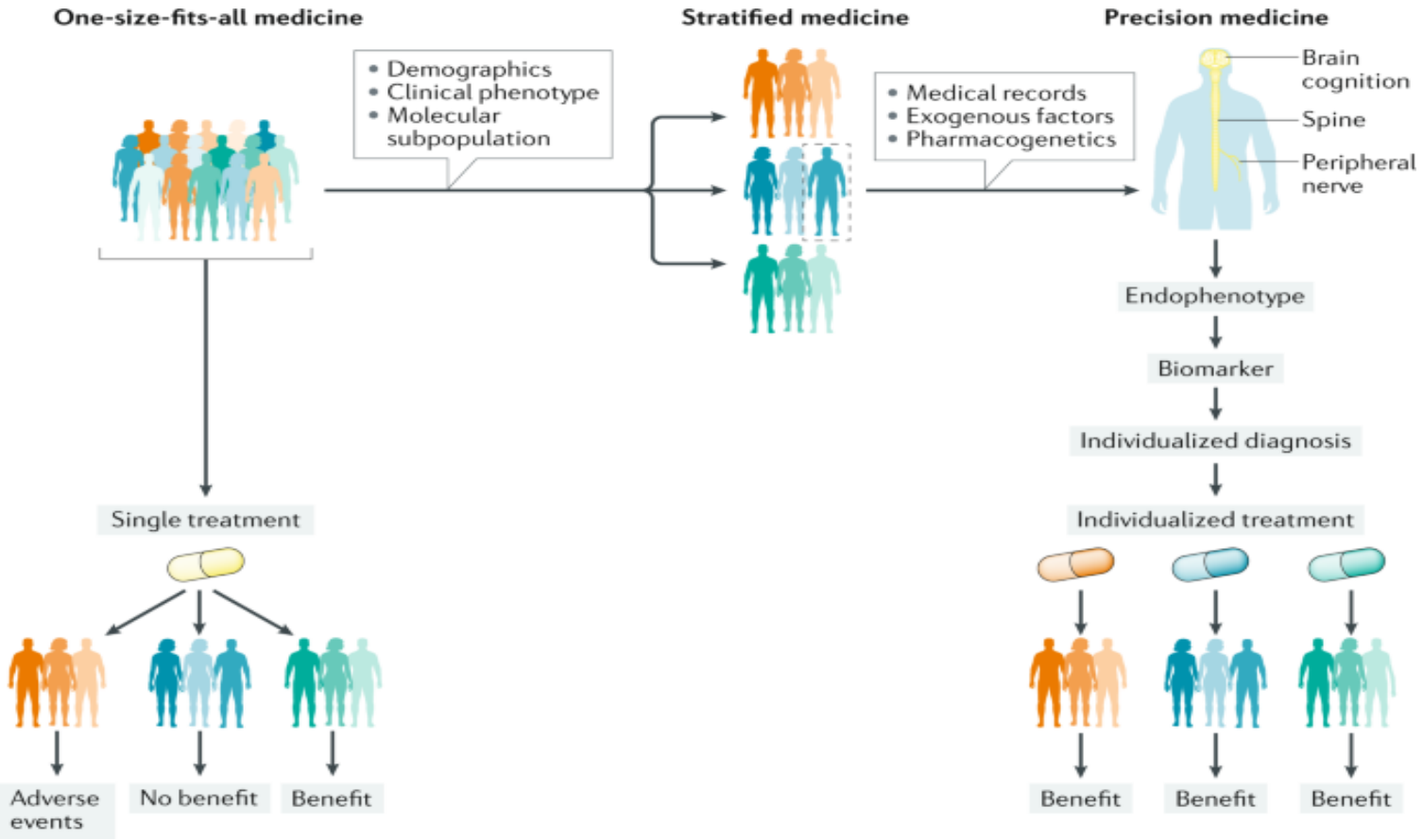




The view in 2021: Druggable molecular pathways to ALS are emerging

Source: Van Damme et al., Dis. Model Mech., 2017

1° Therapy Development Challenge: Disease heterogeneity



Kiernan, M.C., Vucic, S., Talbot, K… Cudkowicz, M *et al*. *Nat Rev Neurol* 17, 104–118 (2021).

Pressing need to innovate ALS trials
(> 160 companies; partial list)

- Toferson
- AMX0035
- Reldesmetiv
- NurOwn
- Methylcobalamin
- Masitinib
- Corestim
- Ibudilast
- Healey ALS Platform Trial Drugs (5)
- TriCALS Platform Trial Drugs (2)
- Ultomiris
- RNS60

- AT501
- Empaveli
- CuATSM
- BIIB105
- BIIB100
- BIIB078
- AP101
- Basis (EH301)
- ABBV-CLS-7262
- ION363
- AstroRX
- Engensis
- IPL344
- ...and more

Early Phase Pipeline Pressure

https://iamals.org/get-help/als-signal-clinical-research-dashboard/

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

How to increase likelihood of success?

Cohort enrichment

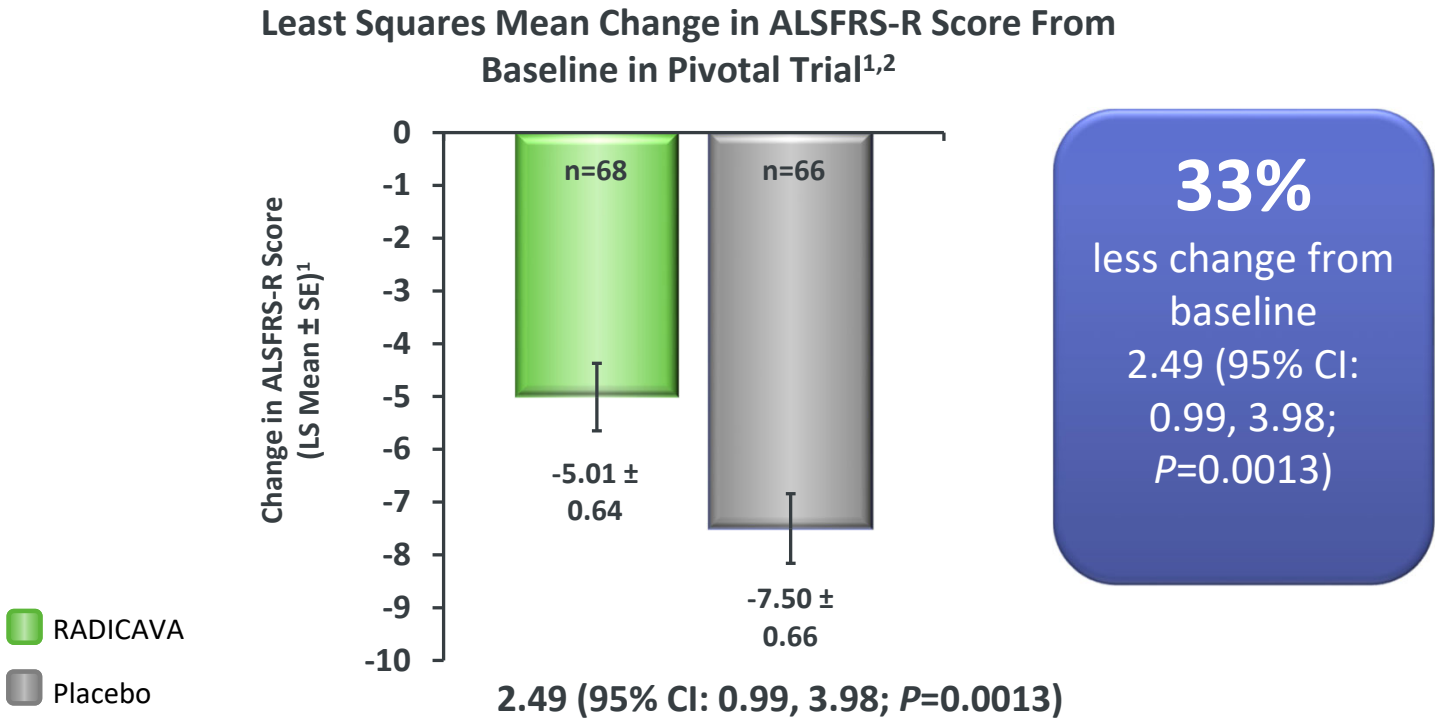
- Homogenous group of study participants
  - *Edaravone (Radicava), AMX0035, NurOwn, Methylcobalamin*

- Biologically more likely to respond to treatment (mechanism-based selection)
  - *SOD1 & C9 & FUS ASO & AAV+ , Retigabine, Lithium, Herv-K+*

Innovative trial approaches

- *Healey Center at Mass General ALS Platform Trial*

RADICAVA™ Demonstrated Statistical Significance on the Primary Endpoint (24 weeks)[1,2]



33%
less change from baseline
2.49 (95% CI: 0.99, 3.98; *P*=0.0013)

CI=confidence interval.

1. RADICAVA ™ (edaravone) Prescribing Information. Jersey City, NJ: MT Pharma America, Inc.; 2017.
2. Data on File. Jersey City, NJ: MT Pharma America, Inc.

Trials were in Early/Rapid ALS. Can We Generalize the Results to Everyone?

Possibility 1: Radicava biologically works better in people with early/rapid ALS

- There may be more inflammation/oxidative toxicity in this subgroup
- We don't have any proof of this

Possibility 2: Studying people with early/rapid ALS just reduced variability and the results apply to all people with ALS?

- Variability between participants makes it challenging to *demonstrate* a drug effect in a trial
- The researchers reduced variability by focusing on a subgroup of patients

Combination of PhENylbutyrate (PB) and TAURursodiol (TURSO)

CENTAUR

Sabrina Paganoni, MD, PhD

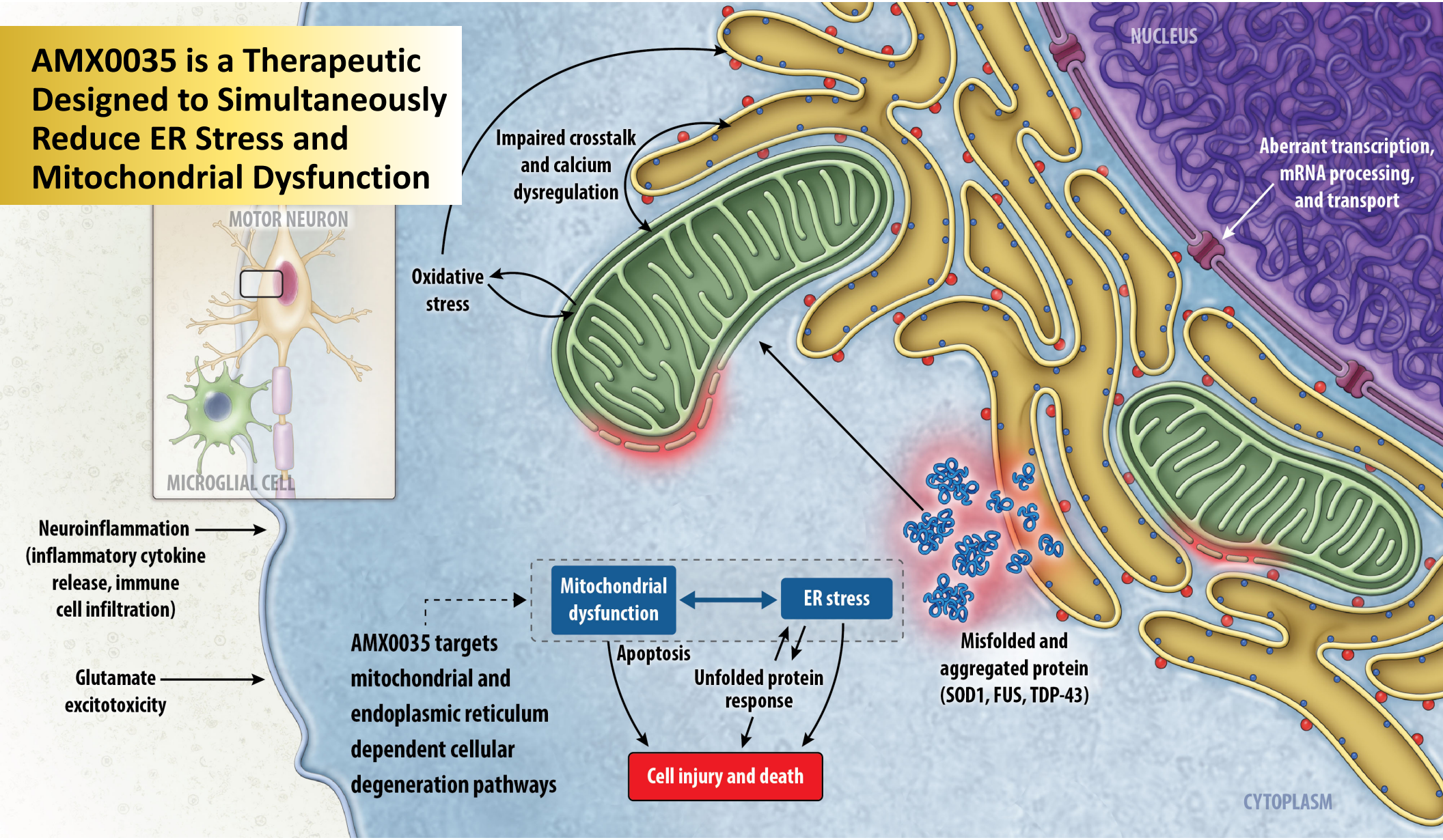
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

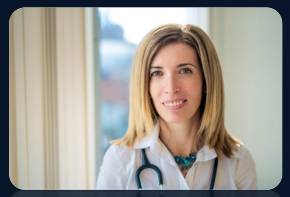
Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis

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

AMX0035 is a Therapeutic Designed to Simultaneously Reduce ER Stress and Mitochondrial Dysfunction



Design:
Randomized Placebo-Controlled Trial



Sabrina Paganoni, MD, PhD

CENTAUR

Screened for eligibility (n=177)

Key inclusion criteria:

- Definite ALS, El Escorial criteria
- <18 months from symptom onset
- Slow vital capacity (SVC) >60%
- **Riluzole and edaravone use allowed**

Randomization 2:1 (n=137)

AMX0035

Placebo

AMX0035 comes in a sachet, is mixed with water, and taken by mouth or via feeding tube

Treatment: 24 weeks

CENTAUR Met Its Primary End Point

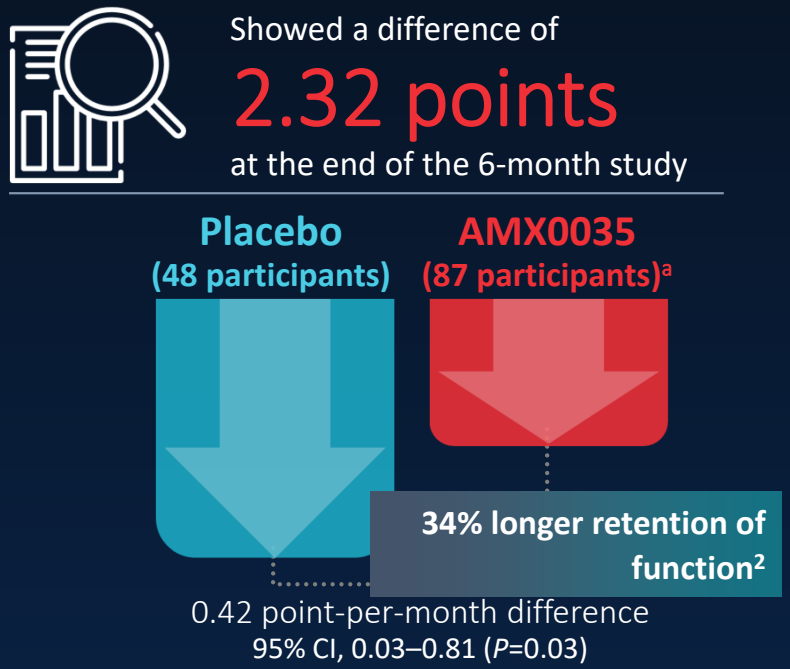
Administration of AMX0035 significantly slowed the rate of decline in ALSFRS-R total score[1]

Shared Baseline Model[1]

Showed a difference of

2.32 points

at the end of the 6-month study

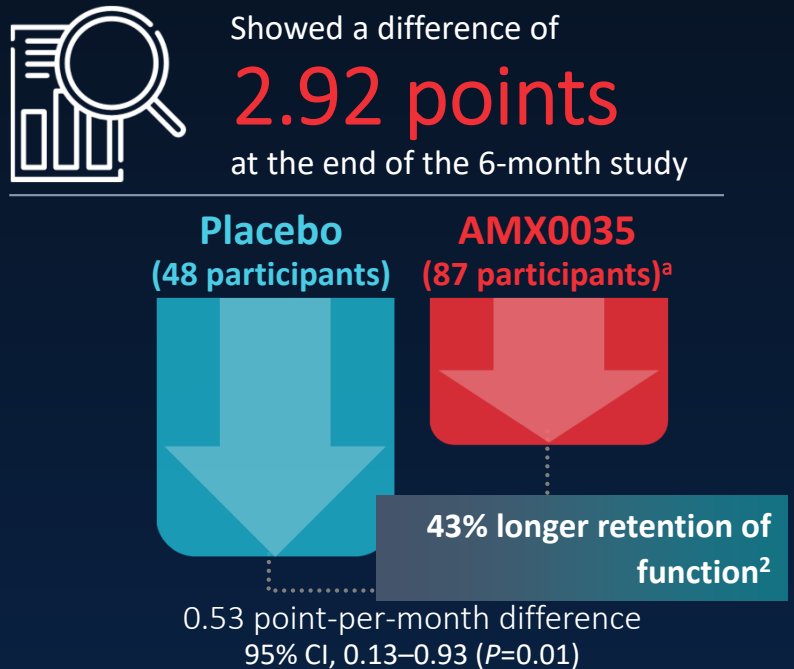


Change From Baseline Model[1]

Showed a difference of

2.92 points

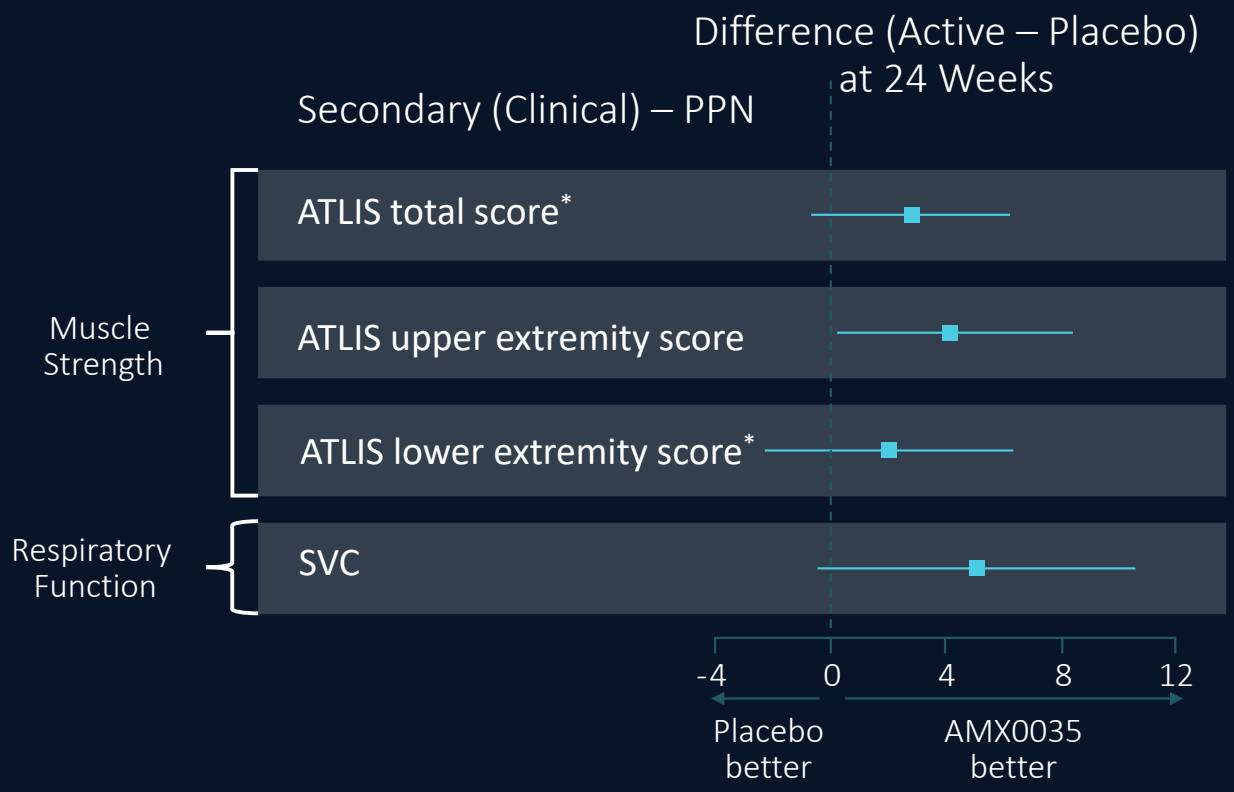
at the end of the 6-month study



[a]2 patients had no follow-up assessment of ALSFRS-R score and hence were excluded for analysis. mITT population included 135 patients.
mITT, modified intent-to-treat.

1. Paganoni S, et al. *NEJM*. 2020;383:919-930. **2.** Data on File. Amylyx Pharmaceuticals.

Impact on Muscle Strength and Respiratory Function



*Number of participants (placebo/active) represented at week 24: 32/55 for total ATLIS, 32/55 for upper ATLIS, and 33/56 for lower ATLIS.
ATLIS Accurate Test of Limb Isometric Strength, SVC slow vital capacity.


CENTAUR
Thank You

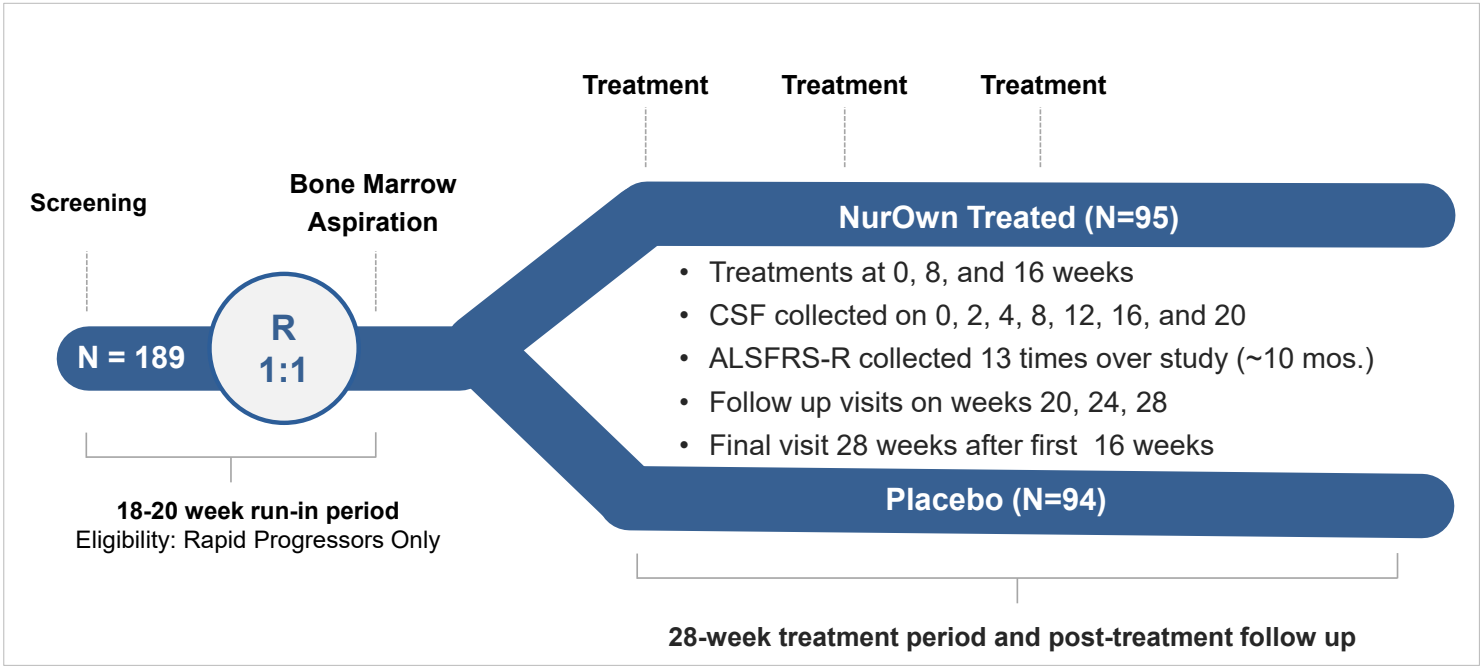
Goal is to get AMX0035 to all people living with ALS worldwide

Conduct a trial that meets requirements for both FDA and the European Agency

- PHOENIX is scheduled to begin in late Summer 2021
- Available both in the US and Europe
- Larger
- Broader inclusion criteria
- Comprehensive set of outcome measures

BCT002: Phase 3 Trial of NurOwn® in ALS Patients

First Participant Screened: 28 August 2017
Database Lock: 30 October 2020



Primary Endpoint

A responder analysis of the rate of decline as assessed by ALSFRS-R

Secondary Endpoints

Safety

ALSFRS-R change from baseline

Combined analysis of Function and Survival

Slow vital capacity

Tracheostomy-free survival

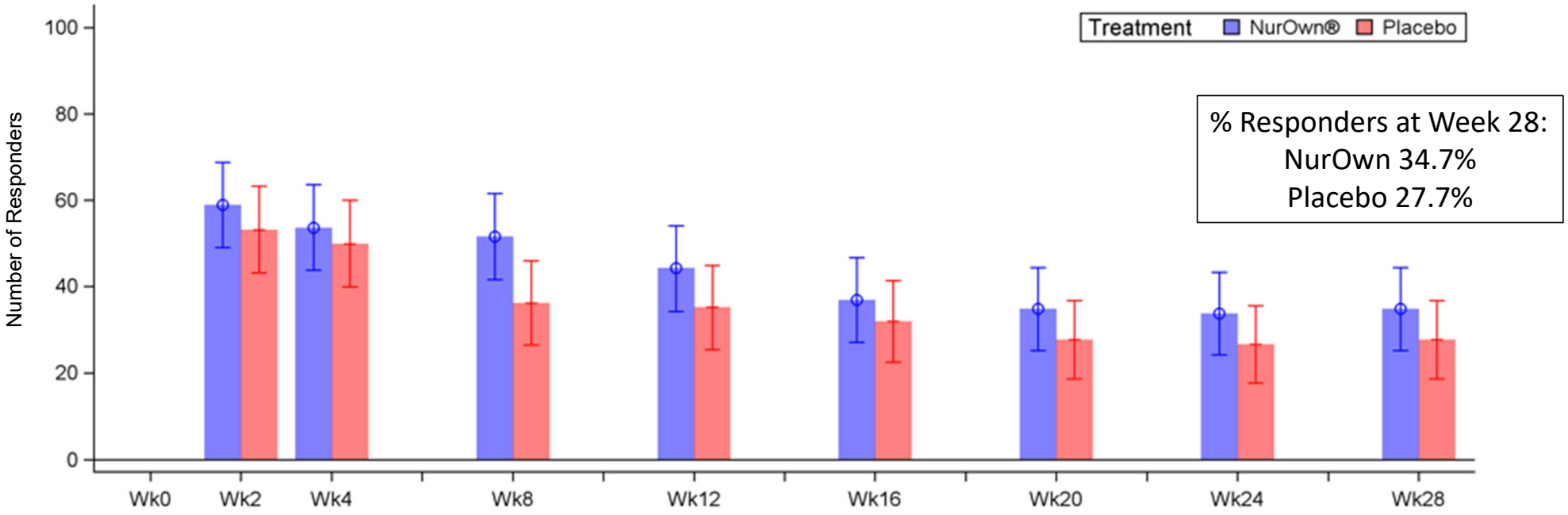
CSF/biomarkers

ClinicalTrials.gov Identifier: NCT03280056

Abbreviations: ALSFRS-R=ALS Functional Rating Scale, revised; CSF=Cerebrospinal fluid

Responder Analysis, Rate of Decline in ALSFRS-R

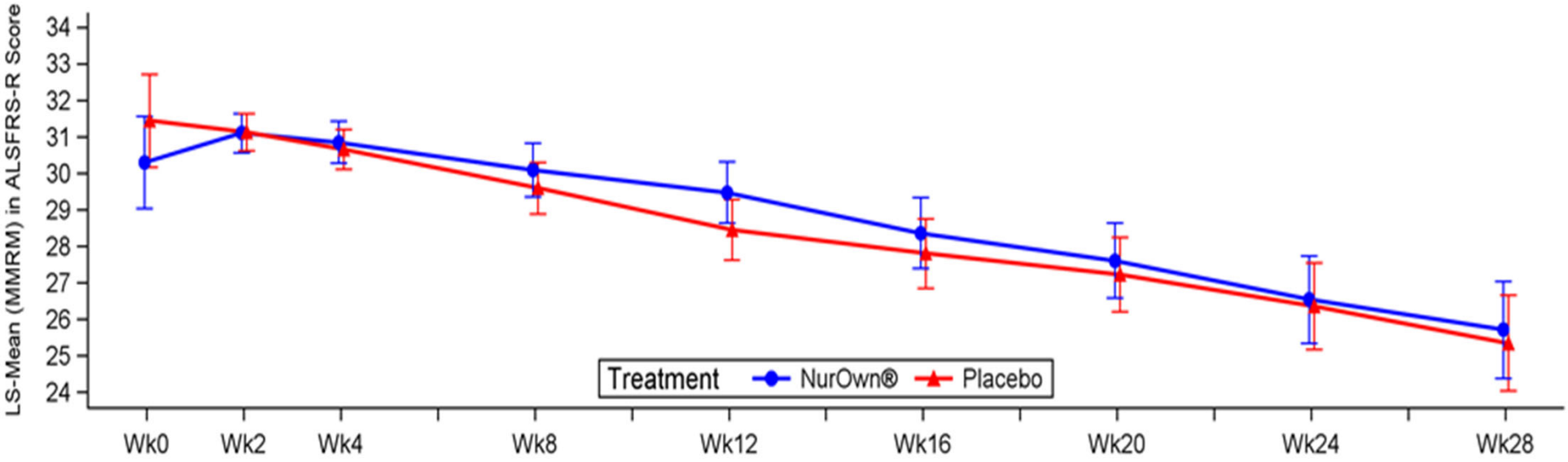
Primary endpoint of Study BCT002



Responder= ≥1.25 points/month improvement in post-treatment slope vs. pre-treatment slope in ALSFRS-R score
Higher percentage of responders in NurOwn group but not statistically significant over placebo (p=0.453)

ALSFRS-R LS Mean (SD) Total Score

Secondary endpoint of Study BCT002

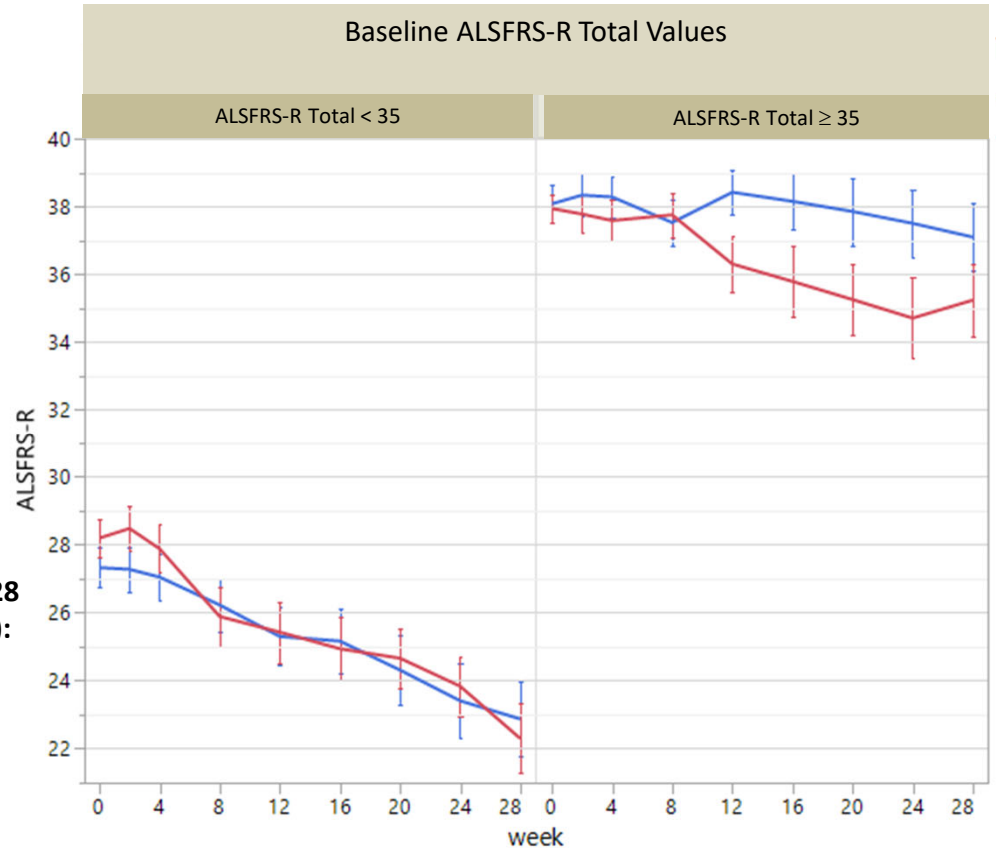


ALSFRS-R LS mean total score based on mixed effects repeated measures model (MMRM)

Mean total score similar for NurOwn and Placebo groups

Mean Change in ALSFRS-R Score from Baseline, by Baseline ALSFRS-R Score

For participants with baseline ALSFRS-R ≥ 35, NurOwn treatment shows a 2-point benefit at 28 weeks
Statistical difference not demonstrated



Baseline ALSFRS-R ≥ 35, Week 28 Difference in LS Means (95% CI):
2.01 (-1.06, 5.08), p=.198

Baseline ALSFRS-R < 35, Week 28 Difference in LS Means (95% CI):
.09 (-2.00, 2.18), p=.933

How to increase likelihood of success?

Cohort enrichment

Homogenous group of study participants

Edaravone (Radicava), AMX0035, NurOwn

Biologically more likely to respond to treatment (mechanism-based selection)

SOD1 & C9 ASO & AAV+ , Retigabine, Lithium, Herv-K

Innovative trial approaches

Healey Center at Mass General ALS Platform Trial

Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

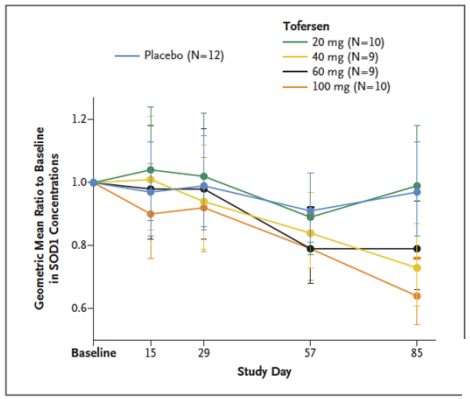
Timothy Miller, Merit Cudkowicz, Pamela J. Shaw, Peter M. Andersen, , Nazem Atassi, Robert C. Bucelli, Angela Genge, Jonathan Glass, Shafeeq Ladha, Albert L. Ludolph, Nicholas J. Maragakis, Christopher J. McDermott, Alan Pestronk, John Ravits, François Salachas, Randall Trudell, Philip Van Damme, Lorne Zinman, C. Frank Bennett, Roger Lane, Alfred Sandrock, Heiko Runz, Danielle Graham, Hani Houshyar, Alexander McCampbell, Ivan Nestorov, Ih Chang, Manjit McNeill, Laura Fanning, Stephanie Fradette, and Toby A. Ferguson

Study sponsored by Biogen
ASO developed in collaboration with Ionis Pharmaceuticals

N Engl J Med
Volume 383(2):109-119
July 9, 2020

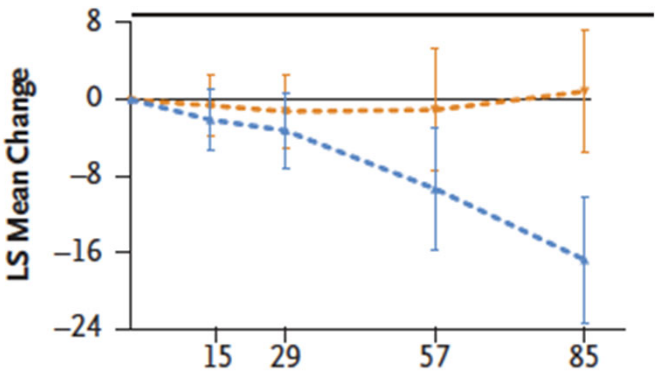
Opportunities to Treat and Prevent ALS
Targeted ASO therapies for genetic and sporadic forms

Suppresses CSF SOD1
(dose dependent)



36%

Slows decline in ALSFRS-R (and SVC)



ESTABLISHED IN 1812 JULY 9, 2020 VOL. 383 NO. 2

Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T. Miller, M. Cudkowicz, P.J. Shaw, P.M. Andersen, N. Atassi, R.C. Bucelli, A. Genge, J. Glass, S. Ladha, A.L. Ludolph, N.J. Maragakis, C.J. McDermott, A. Pestronk, J. Ravits, F. Salachas, R. Trudell, P. Van Damme, L. Zinman, C.F. Bennett, R. Lane, A. Sandrock, H. Runz, D. Graham, H. Houshyar, A. McCampbell, I. Nestorov, I. Chang, M. McNeill, L. Fanning, S. Fradette, and T.A. Ferguson

FUS
C9orf72
Ataxin-2
Stathmin & more coming

Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

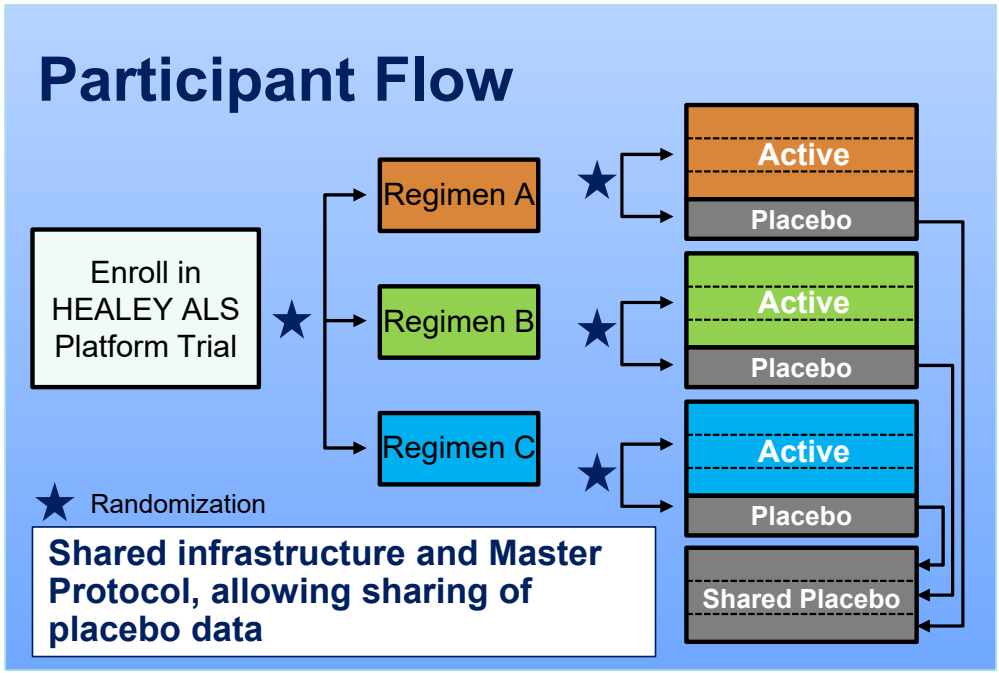
Summary

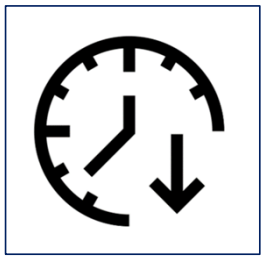
- Administration of multiple doses of tofersen was generally well tolerated
- Reduction in CSF SOD1 in the Tofersen 100 mg group
- Exploratory analyses show a slowing of decline in functional, respiratory, and strength measures
- Exploratory analysis show reduction in neurofilament proteins
- Ongoing Phase 3, Valor Study
  - (ClinicalTrials.gov Identifier: NCT02623699, ALSValorStudy.com)

Small Studies and Post-Hoc Analyses: Why repeat studies are needed sometimes

- Dexpramepexole
- Levosimendin
- Edaravone
- Methylcobalamin

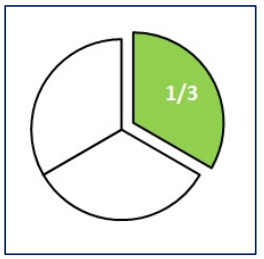
High throughput trials: Platform Trials in ALS bring enormous operational and scientific efficiencies





Cuts time in 1/2

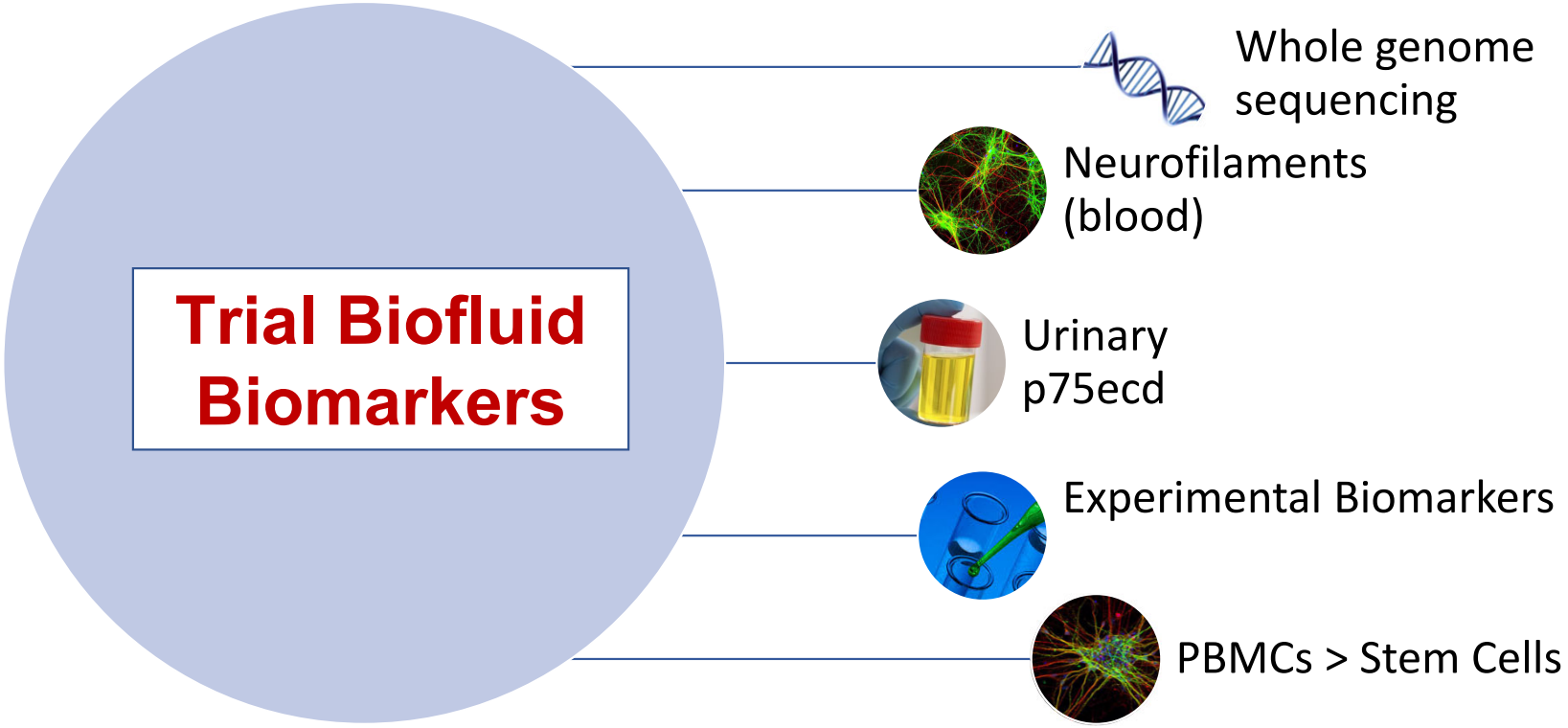
Cuts costs by 1/3



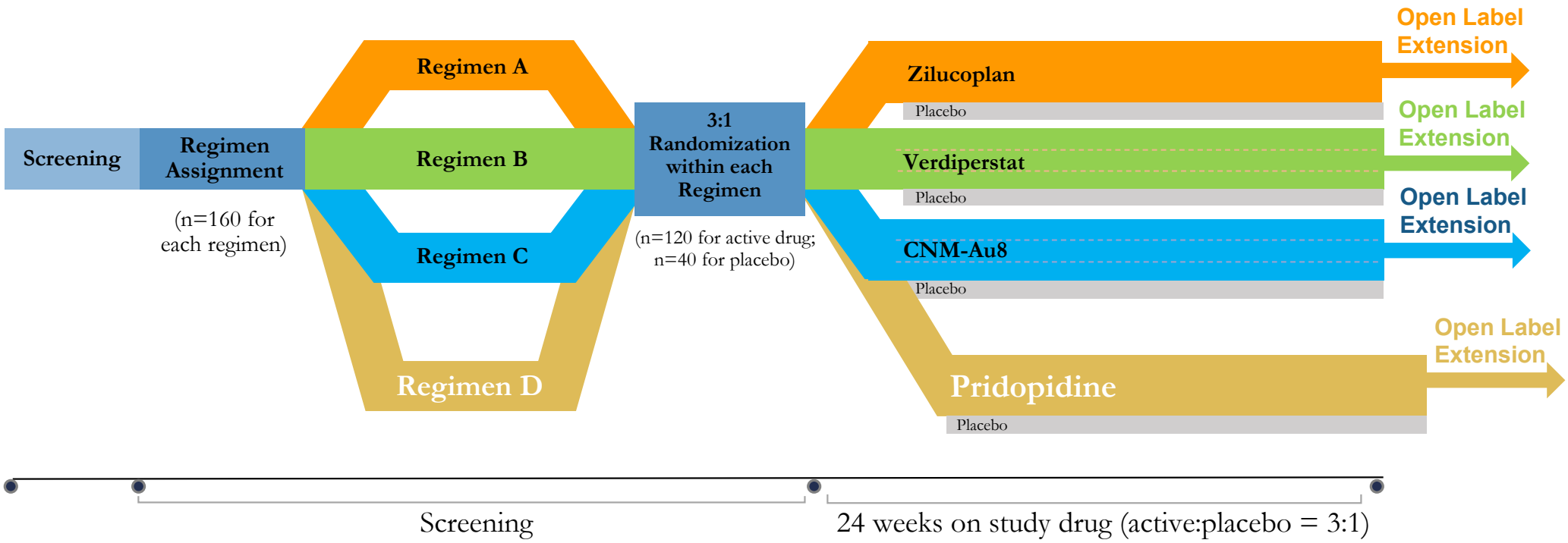
Reduces placebo

HEALEY ALS Platform Trial started July 2020, Led by Mass General

Endpoint Development Engine



HEALEY ALS Platform Trial
Perpetual Adaptive Trial



Enrollment Status of the HEALEY ALS Platform Trial

As of June 7, 2021:

42 sites - 78%! approved by cIRB for Regimen D

52 sites activated for enrollment for Regimen A-C

39 sites activated for enrollment for Regimen D

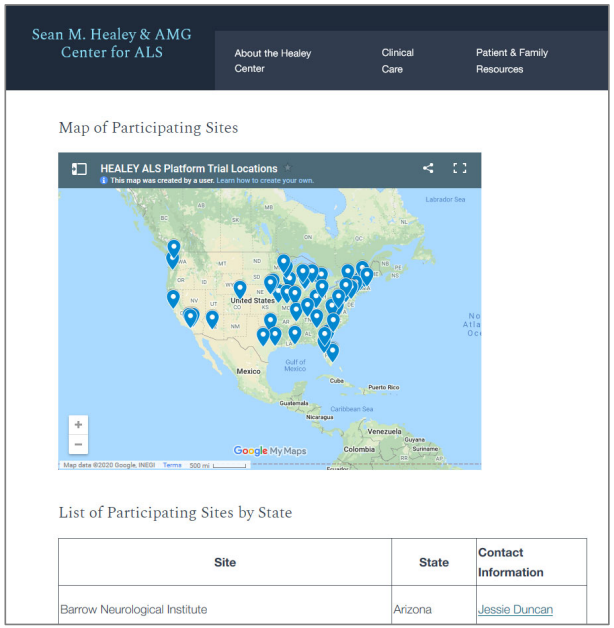
576 participants consented in Master Protocol *(111 in OLE)*

402 participants randomized to a regimen

- 109 RGA
- 127 RGB
- 127 RGC
- 39 RGD

Estimated enrollment completion for Regimen A-C projected in Sept 2021

How to Find a Center Near You



52 sites are actively enrolling

Contact Info of Participating Sites by State

https://www.massgeneral.org/neurology/als/research/platform-trial-sites

as of 4/29/21

Patient Navigator

Catherine Small

Allison Bulat

Phone: 833-425-8257 (HALT ALS)

E-mail:healeyalsplatform@mgh.harvard.edu

List of eligibility criteria online:

https://bit.ly/3p4PrLL

Gupta Family Endowed Prize for Innovation in ALS Care

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

2021 Call for Nominations

- **Release Date:** May 7, 2021
- **Nomination Due Date:** July 2, 2021
- **Notification to successful candidate:** August 2021
- **Presentation of award:** 2021 Annual NEALS Meeting, October 6-8, 2021.

Prize Criteria

The 2021 Gupta Family Endowed Prize is accepting global nominations for teams that made a significant impact on ALS care. There are no limits on the types of solutions to improve care. Examples of ALS care innovation include but are not limited to assistive technology, multidisciplinary care, communication and education, trials, nutrition.

- The project nominated should be realized and ongoing as well as scalable to reach a larger group of people living with ALS within 1 year.
- Nominees should have a touchpoint with patients and/or caregivers.
- Nominations are accepted from all but preference will be given to projects led by junior investigators/teams/clinicians.
- Nominations do not have to be from an academic institution.
- We strongly discourage multiple nominations for the same team as one will suffice.
- While self-nominations are allowed, nominations by others are preferred

Healey Center

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

www.massgeneral.org/neurology/als/research/platform-trial

- **Platform trials can greatly accelerate the path to effective treatments for ALS**
- **There is strong support for the platform approach - regulators, industry, clinician scientists, and patients**
- **This is a perpetual trial and will continue to test more interventions until cures are found for all people with ALS**