CAESAR

Comparative Effectiveness and Safety of Drugs used in Rare Neuromuscular and Neurodegenerative Diseases

CONVEGNO FINALE

7 giugno 2023 - 9.00-17.00

La SLA, una malattia incurabile?

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Ministero dell'Università e della Ricerca

UNIVERSITÀ DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

C.R.E.SLA
Torino

Conflicts of interest

- I serve on scientific advisory boards or speakers bureaus for Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, Zambon, PTC Therapeutics, and Cytokinetics
- I serve as a member of the scientific advisory board for the 5000Genomi@vda
- I serve on Drug Safety monitoring Board for ABScience and Eli Lilly

ARTICLE OPEN ACCESS

Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials

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Neurology® 2019;92:e1-e14. doi:10.1212/WNL.0000000000007242

This process generated a final list of 112 guidelines. Because of the large number of guidelines generated, the section leaders and conference organizers were asked to prioritize 15 guidelines with the greatest potential to improve ALS clinical research. These high-priority guidelines are summarized in the results section below. Section 9 on statistical guidelines was not developed using the modified Delphi process.

Regulatory authority suggestions: EMA

- ***Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (EMA, June 2016)***

  - Trial duration depends on the expected rate of progression which in turn depends on the population included. **Study duration of 12-18 months may be sufficient**. However, it is recommended to check during the trial whether the progression rates are in accordance with the assumptions. Such a blinded interim analysis should only be used for sample size re-estimation if necessary but not for stopping the trial for efficacy. Moreover, an extended follow-up may be needed to generate further survival data (see section on endpoints and methodological considerations below).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

TRICALS

Regulatory authority suggestions

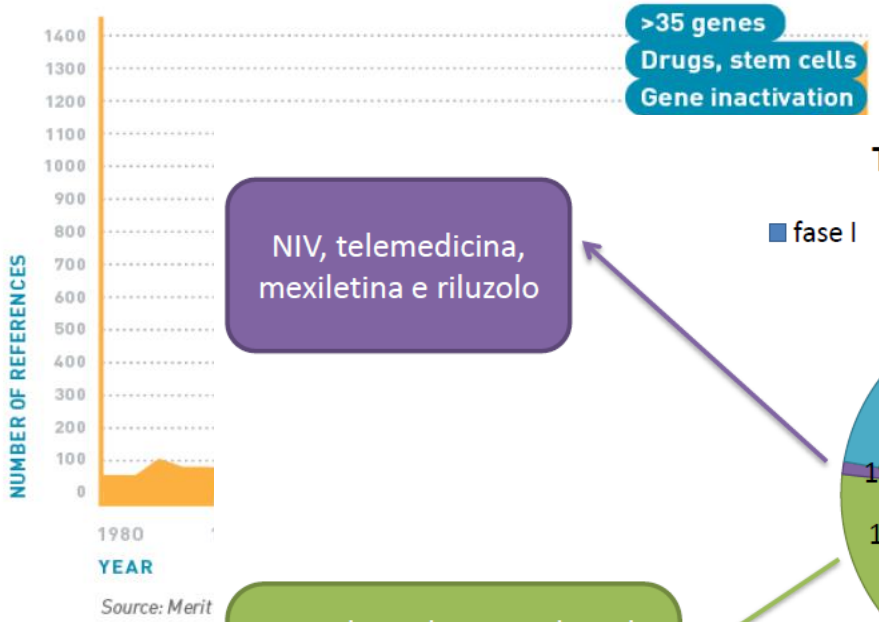
- ***Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry (FDA, September 2019)***
    - Given the typically rapid progression of disease in ALS patients (recognizing considerable heterogeneity in the course of individual patients), it is feasible and most efficient to establish a clinical benefit based on clinical endpoints capable of supporting full approval, even if the benefit is modest. In general, **that benefit can be established in trials of practicable size and duration** (i.e., **6 to 12 months**).

FDA U.S. FOOD & DRUG ADMINISTRATION

TRICALS

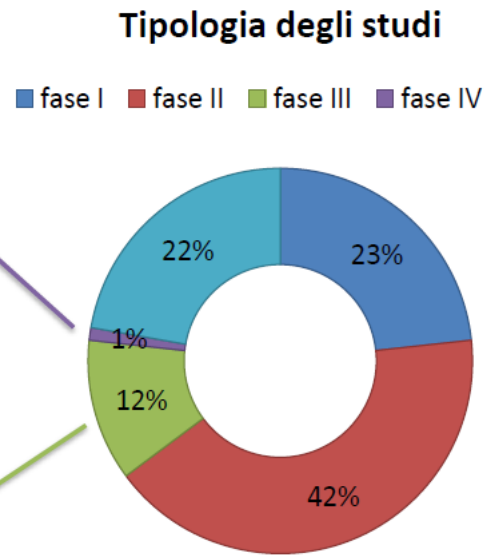
ALS Research Accelerates

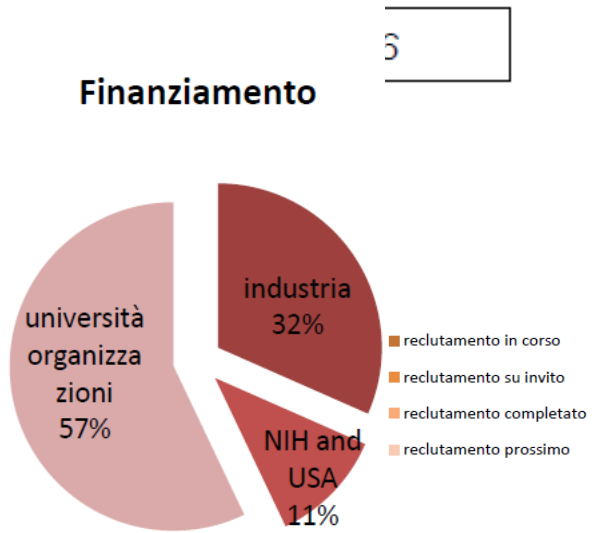
As the decades have seen discoveries in ALS—genes such as SOD1, FDA approval of riluzole—the number of publications about ALS has exploded.



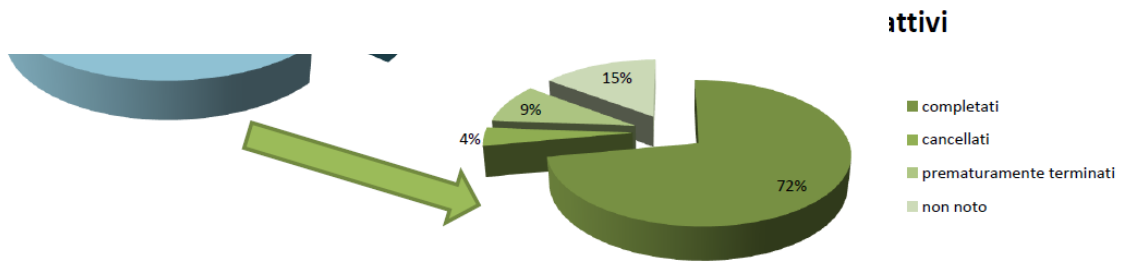
NIV, telemedicina, mexiletina e riluzolo

cannabinoidi, arimoclomol, tirasemtiv, levosimendan, masitinib, metilcobalamina, nerown, deferiprone





Clinicaltrials.gov Dec 2018



Clinicaltrials.gov Dec 2018

Obstacles toward an effective therapy in ALS

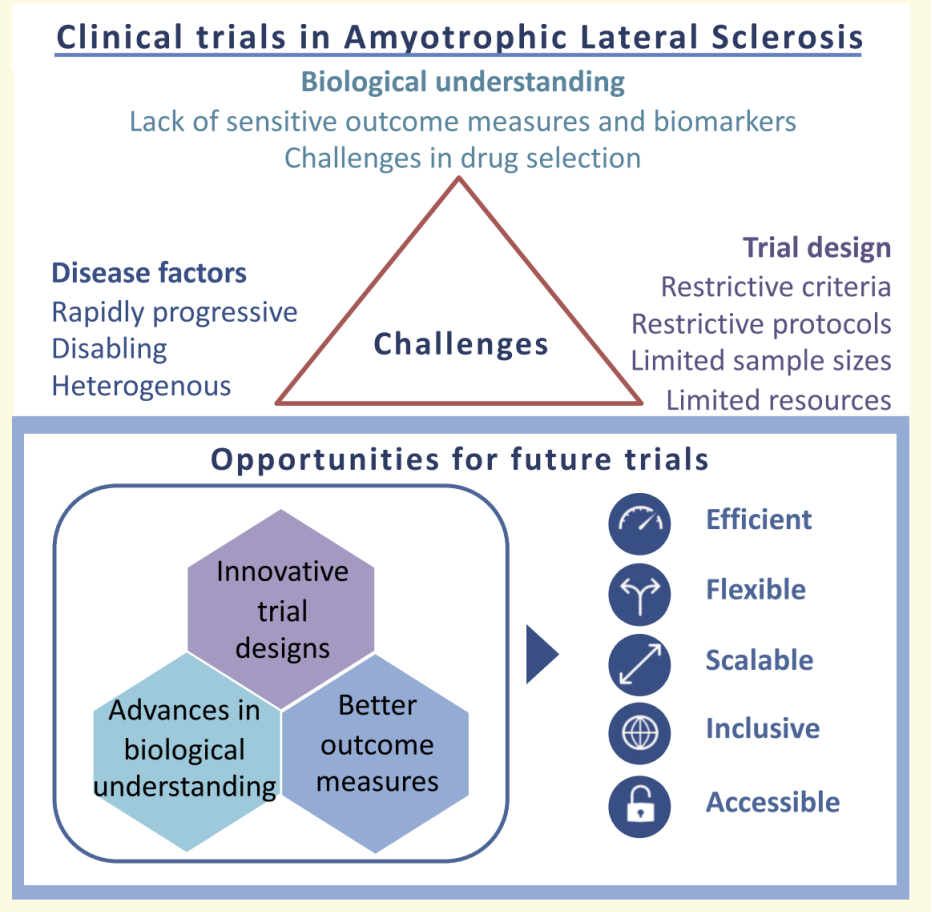
Biological understanding

Lack of effective preclinical models

Clinical and biological heterogeneity

Pitfall in trials design, including the absence of a biomarker

May NfL be the right biomarker?

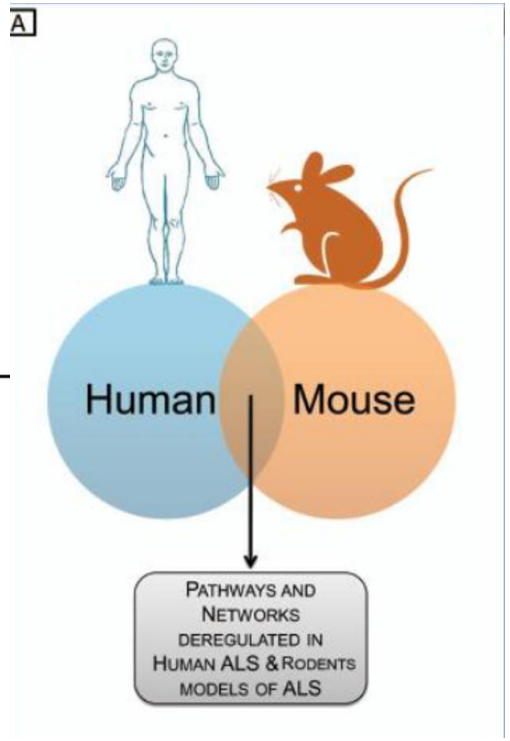


Wong et al, Brain Commun 2022

Pitfalls of ALS clinical trials in ALS

Table 1
Possible reasons for negative results of ALS RCTs.

1. Rationale	Insufficient overall rationale
	Insufficient, negative or misinterpreted data from pre-clinical models
	Misinterpretation of phase 1 or 2 findings
	Excessive reliance on post-hoc analysis of phase 1 or 2 findings
2. Pharmacological issues	Inadequate drug passage of the brain-blood barrier
	Pharmacological interaction (riluzole, other drugs)
	Inadequate dose (too low)
	Drug not tolerated at the active dose (drug toxicity)
	Inadequate pharmacokinetics
	Pharmacogenetics issues
3.Trial design issues	Insufficient statistical power (sample size calculation)
	Inadequate number of patients enrolled
	Inadequate length of trial
	Inadequate inclusion/exclusion criteria
	Imbalance of concurrent treatments (riluzole, other drugs)
	Failure of randomization (imbalance of treatment arms)
	Heterogeneity of sample population (Phenotypic heterogeneity; Inclusion of long survivors; Inclusion of too advanced patients)
	Lack of pharmacological biomarkers (demonstration of the biological effect of the drug)
	Lack of biomarkers sensitive to disease progression
	Non-generalizability of enrolled population
	Inadequacy of measures of efficacy (see Table 2)
	Different population from phase 2 to phase 3
	Heterogeneity of patients' care by recruiting centers (lack of multidisciplinary treatment group)
	Excessive numbers of dropouts/premature discontinuations



Chiò et al, Neuropharmacology 2020

Outcome measures in ALS clinical trials

Table 2
Measures used as endpoint in ALS clinical trials.

Clinical biomarkers	Survival (time to death, tracheostomy o full time non-invasive respiratory support)
	ALSFRS-R
	Muscle Strength Testing
	Respiratory measures (FCV, SVC, Snip)
	Bulbar-specific measures
	Composite markers (Combined Assessment of Function and Survival, CAFS)
Neurophysiological biomarkers	Neurophysiological Index
	Motor unit estimation (MUNIX)
	Electrical impedance myography (EIM)
Muscle imaging	Magnetic Resonance Imaging
	Muscle ultrasound
Staging	King's staging
	MiToS staging
'Wet' biomarkers	Creatine
	Albumin
	Neurofilaments
Neuropsychological markers	Neuropsychological battery, ECAS
Neuroimaging biomarkers	Brain and spinal cord MRI
	Brain and spinal cord PET

Chiò et al, Neuropharmacology 2020

Why biomarkers for ALS trials?

- Biomarkers for patients' stratification

- Biomarkers measuring the biological effect of the investigational drug
  - Crucial for phase I and II trials

- Biomarkers sensible to disease progression
  - Reliable proxy of clinical measures
  - Easily assessable throughout the trial
  - Affordable in each centre
  - Non-invasive as possible for the patient

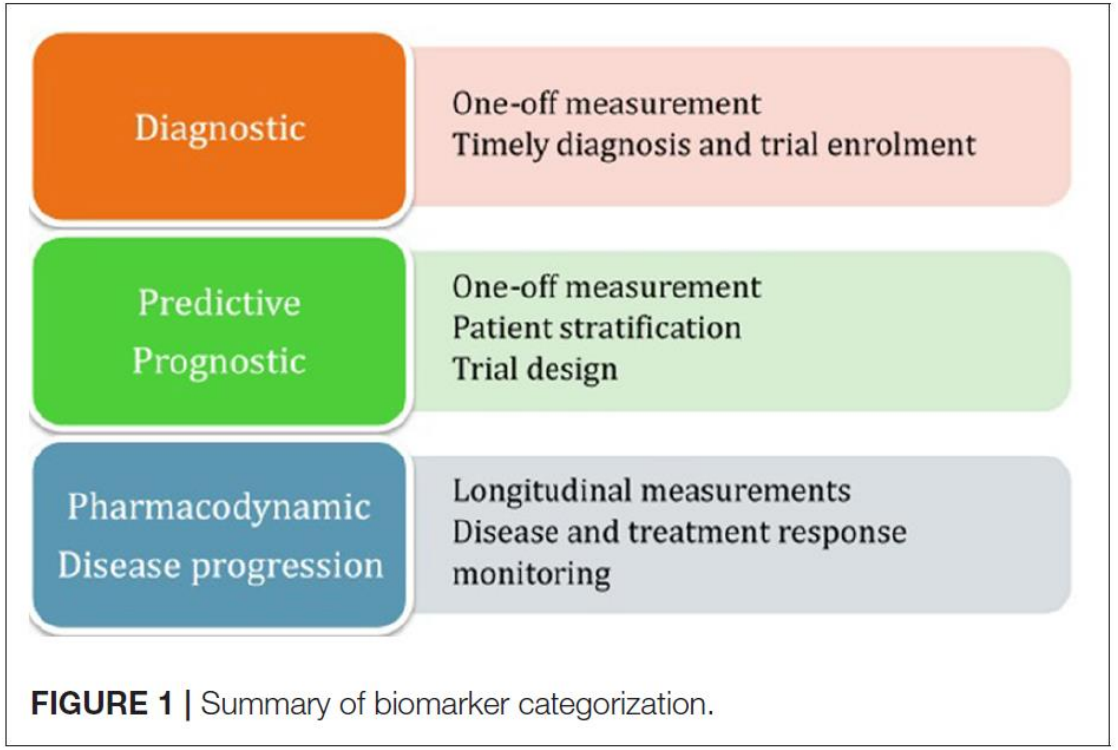
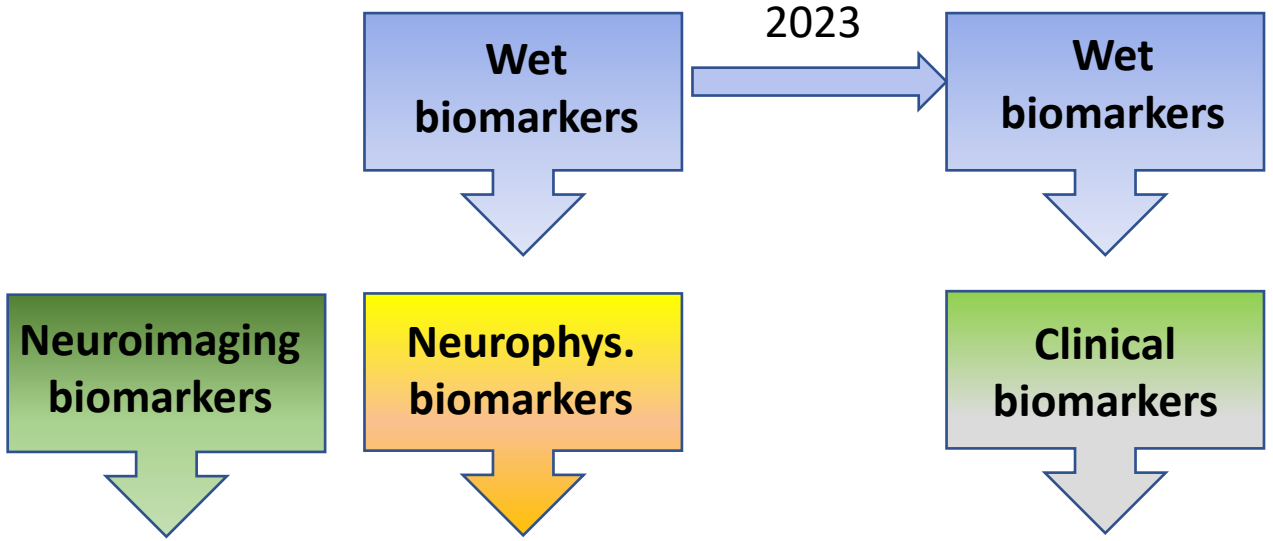


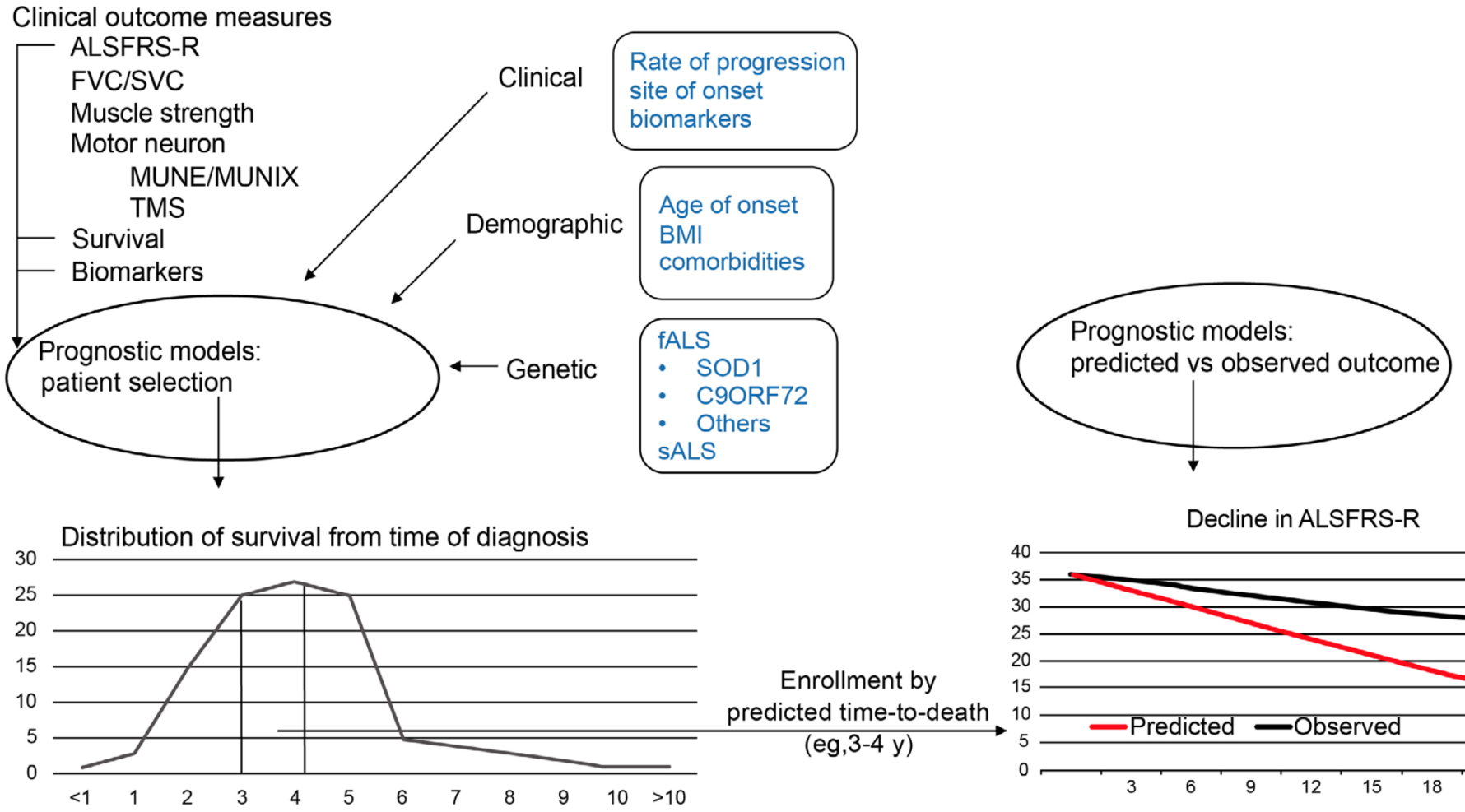
FIGURE 1 | Summary of biomarker categorization.

Outcome measures in ALS: where are we now?



FDA Advisory Committee statement plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS

Heterogeneity of ALS



Possible reasons for negative results of trials in ALS

- Rationale
  - Inadequate drug passage of the blood-brain barrier
  - Pharmacological interactions (riluzole, edaravone, other drugs)
  - Inadequate dose (too low)
  - Drug not tolerated at the active dose (drug toxicity)
  - Inadequate pharmacokinetics
  - Pharmacogenetics issues

Chiò et al, Neuropharmacology 2020

Possible reasons for negative results of trials in ALS

- Pharmacological issues
  - Insufficient overall rationale
  - Insufficient, negative or misinterpreted data from studies on preclinical models
  - Misinterpretation of phase 1 or 2 trial findings
  - Excessive reliance on post-hoc analysis of phase 1 or phase 2 trial findings

Chiò et al, Neuropharmacology 2020

Possible reasons for negative results of trials in ALS

- Trial design issues
  - Insufficient statistical power
  - Inadequate number of patients enrolled
  - Inadequate length of trial
  - Inadequate exclusion/inclusion criteria
  - Imbalance of concurrent treatments (riluzole, other)
  - Failure of randomization (imbalance of treatment arms)
  - Heterogeneity of sample population (phenotypic heterogeneity, inclusion of long survivors, inclusion of excessively advanced patients)
  - Lack of pharmacological biomarkers (insufficient demonstration of the biological effect of the drug)
  - Use of biomarkers insensitive to disease progression
  - Non-generalizability of enrolled population
  - Inadequacy of measure of efficacy
  - Different populations from phase 2 to phase 3
  - Heterogeneity of patients' care by recruiting centers (lack of multidisciplinary treatment team)
  - Excessive number of drop-outs / premature discontinuations

Chiò et al, Neuropharmacology 2020

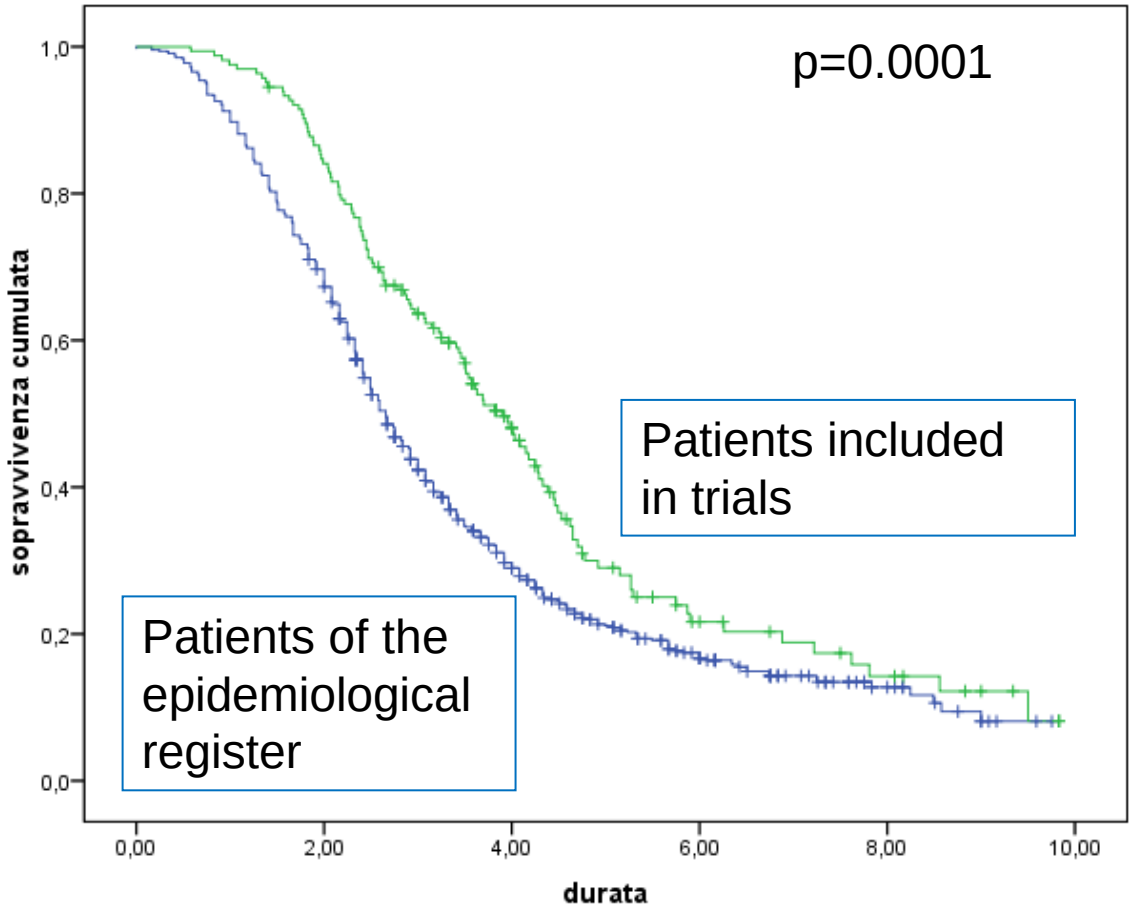
Can clinical trial results extended to the whole ALS population?

Difference between patients enrolled in trials and registry patients

	Patients enrolled in clinical trials (n=164)	Patients included in the PARALS (overall) (n=813)	Patients included in the PARALS (trial entry criteria) * (n=568)	p (trials vs. PARALS)	p (trials vs. PARALS entry criteria)
Mean age at onset, years (SD)	56.2 (10.2)	65.1 (11.1)	62.0 (9.5)	0.0001	0.0001
Mean onset-diagnosis delay (SD)	13.1 (9.3)	10.1 (8.9)	9.4 (8.1)	0.003	0.0001
Bulbar onset (%)	25 (15.2%)	266 (32.7%)	176 (31.0%)	0.0001	0.0001
Women (%)	61 (37.2%)	380 (46.7%)	267 (47.0%)	0.04	0.02
Frequency (%) of fALS	14 (8.5%)	39 (4.8%)	29 (5.1%)	0.05	0.05

Chiò et al. ALS clinical trials: do enrolled patients accurately represent the ALS population? Neurology 2011

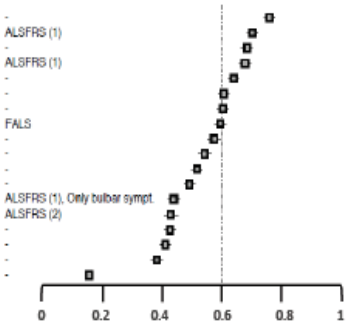
Difference of survival between patients recruited in trials and patients in the Piemonte ALS register



Chiò et al. ALS clinical trials: do enrolled patients accurately represent the ALS population? Neurology 2011

2000 – 2010

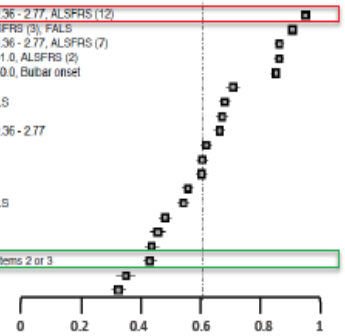
Treatment	Year	Phase	Size	El Escorial	FVC	Symp. dur.	Age	Other:
Pentoxifylline	2006	II	400	Def, Prob	≤ 100%	6 - 47	18 - 80	-
Xaliproden	2004	III	2077	Def, Prob	≥ 60%	6 - 60	18 - 75	ALSFRS (1)
Erythropoietin	2009	II	23	Def, Prob	≥ 70%	0 - 36	18 - 75	-
Glatiramer	2009	II	366	Def, Prob (LS)	≥ 70%	0 - 36	18 - 70	ALSFRS (1)
Valproic acid	2009	II	163	Def, Prob (LS)	≥ 70%	6 - 36	18 - 75	-
Creatine	2003	III	175	Def, Prob (LS)	≥ 60%	6 - 60	18 - 75	-
IGF-I	2008	III	330	Def, Prob	≥ 60%	0 - 30	≥ 18	-
Minocycline	2007	III	412	Def, Prob (LS)	≥ 75%	0 - 36	21 - 85	FALS
Vitamin E	2001	III	288	Def, Prob	≥ 60%	-	≥ 18	-
TCH346	2007	III	543	Def, Prob (LS)	≥ 70%	0 - 36	21 - 80	-
Topiramate	2003	II	294	Def, Prob	≥ 50%	0 - 36	18 - 80	-
Creatine	2004	II	104	Def, Prob	≥ 50%	0 - 60	18 - 80	-
Gabapentin	2001	III	204	Def, Prob (LS)	≥ 60%	0 - 36	21 - 85	ALSFRS (1), Only bulbar sympt.
Indinavir	2005	II	46	Def, Prob (LS)	≥ 50%	-	18 - 85	ALSFRS (2)
CoQ10	2009	II	150	Def, Prob (LS)	≥ 60%	0 - 36	21 - 85	-
Vitamin E	2005	II	160	Def, Prob	-	0 - 60	≥ 18	-
Creatine	2008	II	107	Def, Prob (LS)	-	0 - 60	21 - 80	-
Celecoxib	2006	II	300	All	≥ 60%	0 - 60	≥ 18	-



Exclusion Rate: 0.53 (0.45–0.62)

2010 – 2017

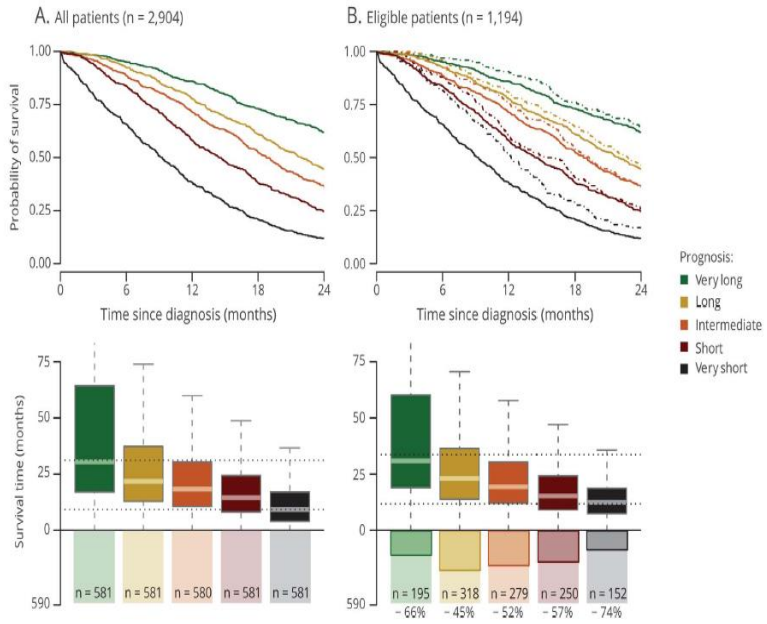
Treatment	Year	Phase	Size	El Escorial	FVC	Symp. dur.	Age	Other:
Edaravone	2017	III	137	Def, Prob	≥ 80%	0 - 24	20 - 75	LI 0.36 - 2.77, ALSFRS (12)
Acetyl-L-carnitine	2013	II	82	Def, Prob (LS)	≥ 60%	6 - 24	40 - 70	ALSFRS (3), FALS
Edaravone	2014	II	205	Def, Prob (LS)	≥ 70%	0 - 36	20 - 75	LI 0.36 - 2.77, ALSFRS (7)
Memantine	2010	II	63	Def, Prob (LS)	≥ 60%	0 - 36	18 - 75	LI >1.0, ALSFRS (2)
TUDCA	2016	II	29	Def, Prob	≥ 75%	0 - 18	18 - 75	LI >0.0, Bulbar onset
Pioglitazone	2012	II	218	All	50%-95%	6 - 36	≥ 18	-
Erythropoietin	2015	III	200	Def, Prob (LS)	≥ 70%	0 - 18	18 - 75	FALS
Olesoxime	2014	III	512	Def, Prob (LS)	≥ 70%	6 - 36	18 - 80	-
Bromocriptine	2016	II	36	All	≥ 70%	0 - 36	20 - 75	LI 0.36 - 2.77
Lithium	2012	II	133	Def, Prob (LS)	≥ 70%	6 - 36	18 - 85	-
Flecainide	2015	II	54	Def, Prob	≥ 50%	0 - 60	18 - 75	-
NP001	2015	II	136	Def, Prob	≥ 70%	0 - 36	21 - 80	-
Talampanel	2010	II	59	Def, Prob	≥ 60%	0 - 24	18 - 85	-
G-CSF	2010	II	39	Def, Prob	≥ 50%	0 - 72	18 - 85	FALS
Lithium	2013	III	214	All	≥ 60%	6 - 36	≥ 18	-
Ozanezumab	2017	II	303	All	≥ 65%	0 - 30	18 - 80	-
Dexpramipexole	2013	III	942	All	≥ 65%	0 - 24	18 - 80	-
Tirasemtiv	2016	II	388	All	≥ 50%	-	≥ 18	>4 items 2 or 3
Lithium	2010	II	84	All	≥ 60%	0 - 36	≥ 18	-
Ceftriaxone	2014	III	513	All	≥ 60%	0 - 36	≥ 18	-



Exclusion Rate: 0.65 (0.54–0.75)

Pooled Exclusion Rate: 0.60 (0.53–0.67)

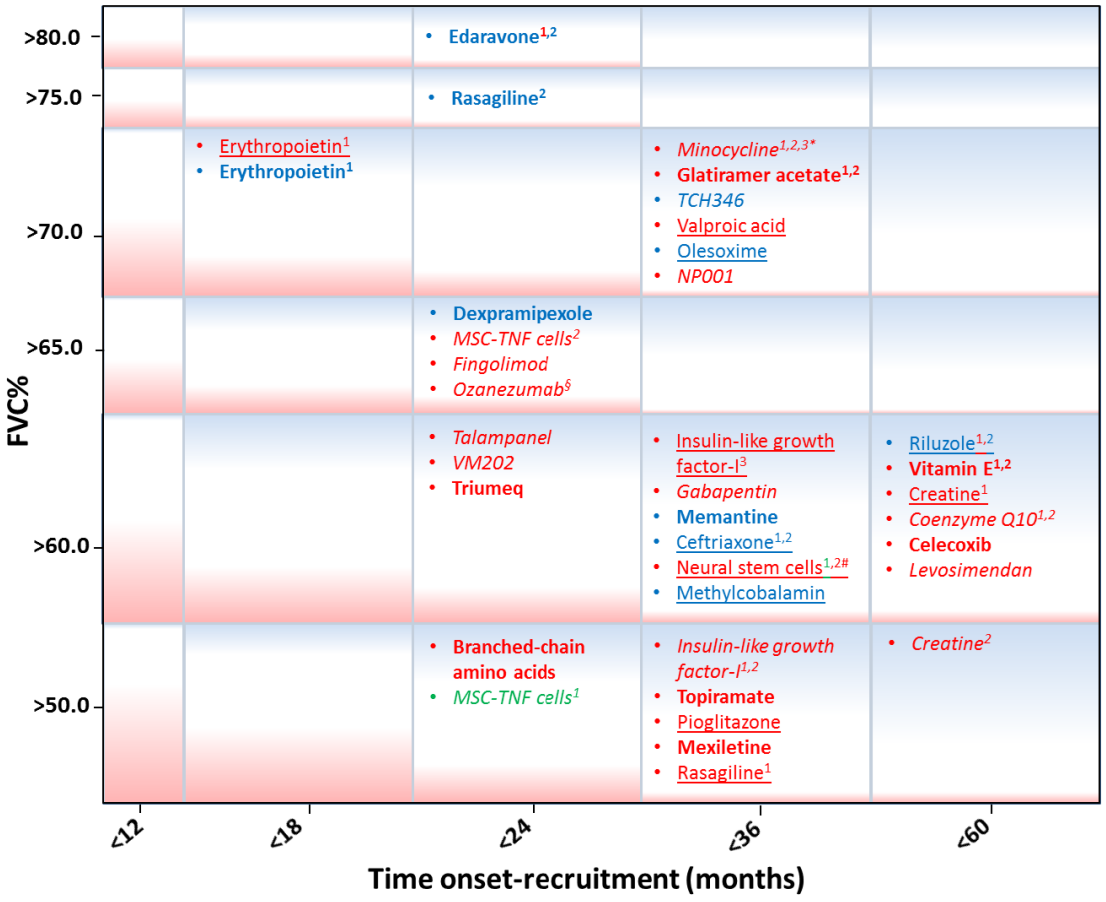
- Large variability in exclusion between trials
  - Edaravone: >90%
  - Tirasemtiv: <50%



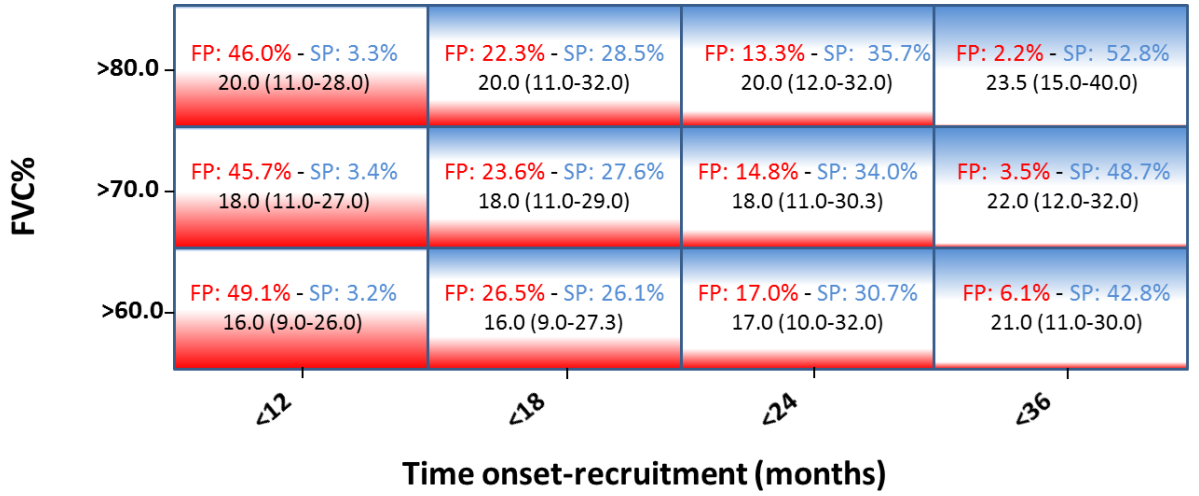
- Exclusion rates range between 30 and 95% and tend to be higher in more recent trials
- Used eligibility criteria reduce the heterogeneity in survival by only 6.9% (i.e. median survival time from 22 to 20.5 months)
- Both fast- and slow-progressors are enrolled

Van Eijk et al. Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials. Neurology 2019

Trial enrollment criteria determine patients' selection



Study population: patients of the Piemonte ALS register, 2000-2017

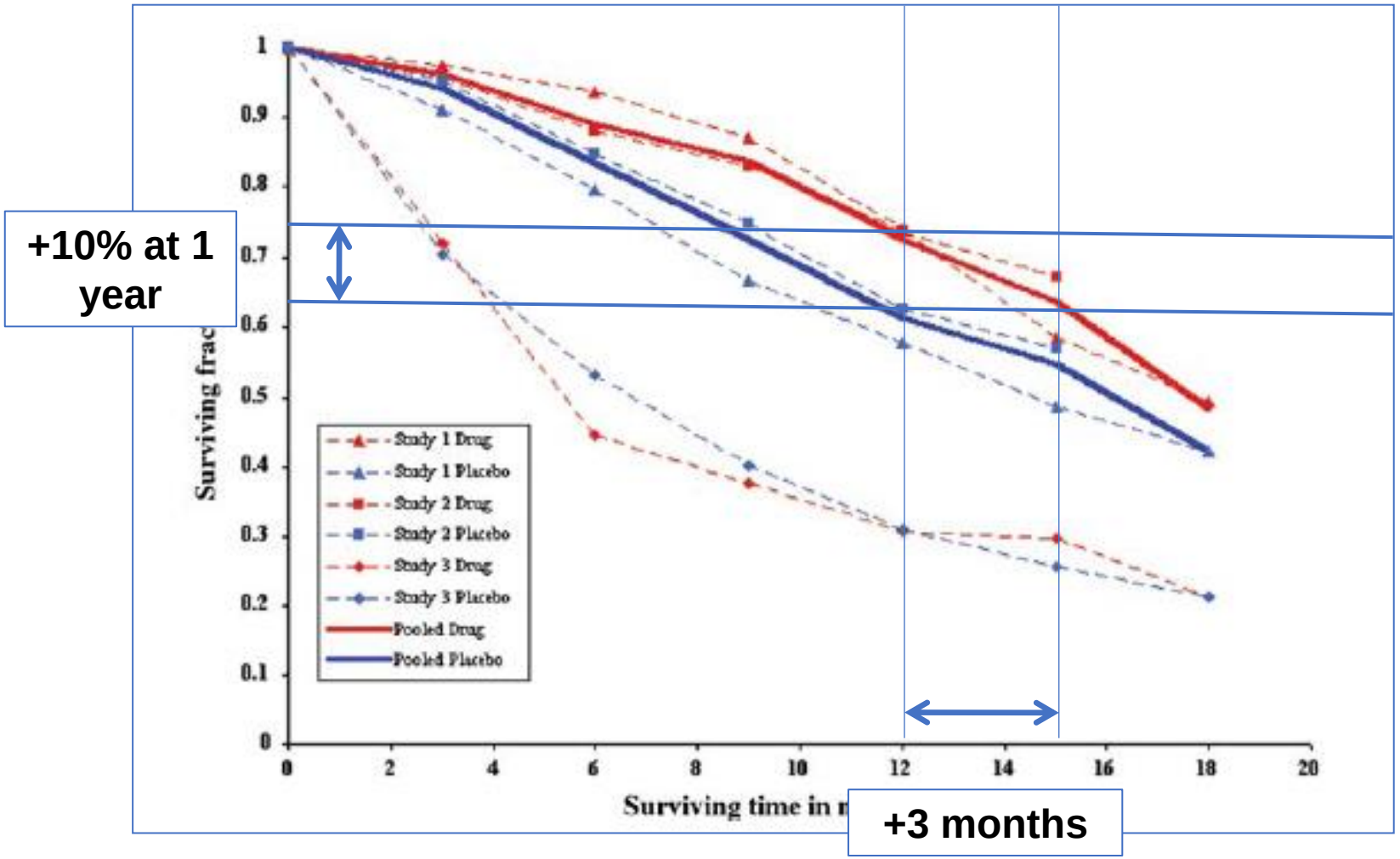


Blue: Slow progressors (ΔALSFRS <0.3)
White: Intermediate progressors (ΔALSFRS between 0.3-0.9)
Red: Fast progressors (ΔALSFRS >0.9)

Torrieri et al. Tailoring patients' enrollment in ALS clinical trials: the effect of disease duration and vital capacity cutoffs. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2021

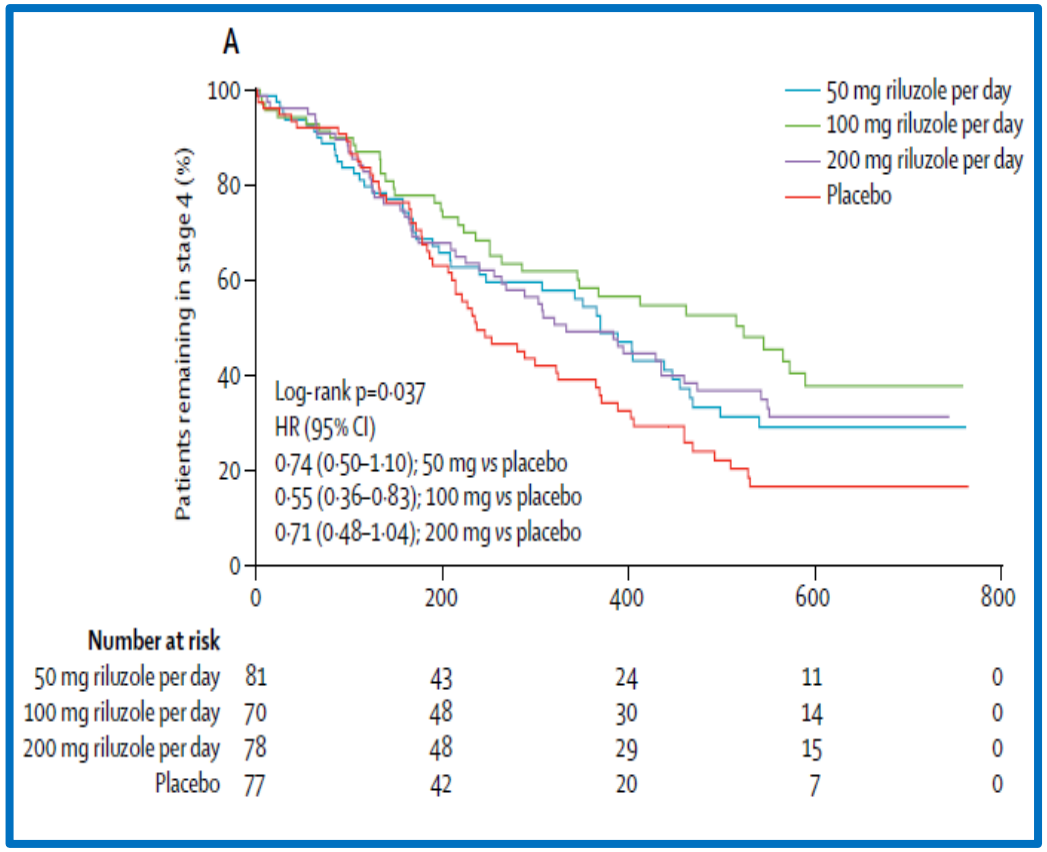
Available disease-modifying therapies for ALS

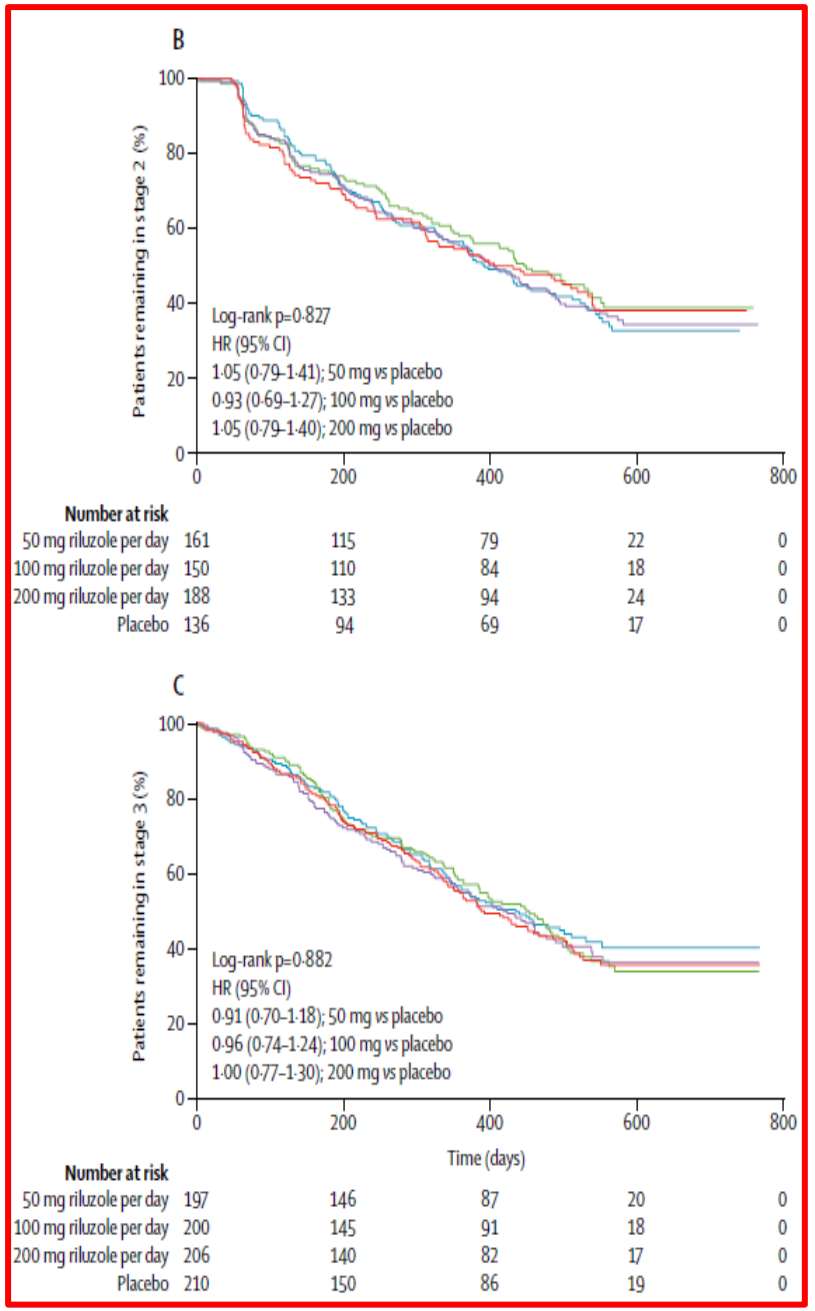
Riluzole - 1997



Riluzole

Retrospective analysis on the original trial





Fang et al, Lancet Neurol 2018

Edaravone

Mechanism of action

- Free radical scavenger
- Marketed in Japan in 2002 for acute treatment of ischemic stroke
- Positive findings in preclinical models (*SOD1 mouse*, Ito et al, 2008; *wobbler mouse*, Ikeda & Iwasaki, 2015)
- Biological marker: reduction of 3-nitrosine in CSF in patients in phase II study (however, the analysis was not repeated in subsequent studies) (Yoshino & Kimura, 2006)

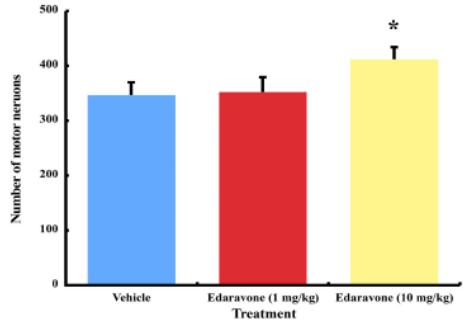
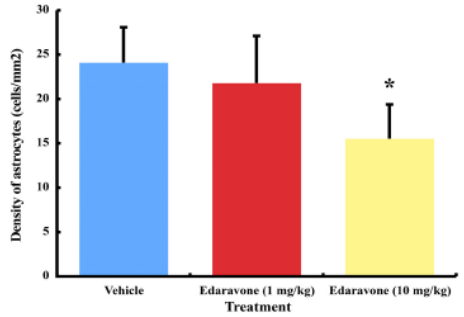
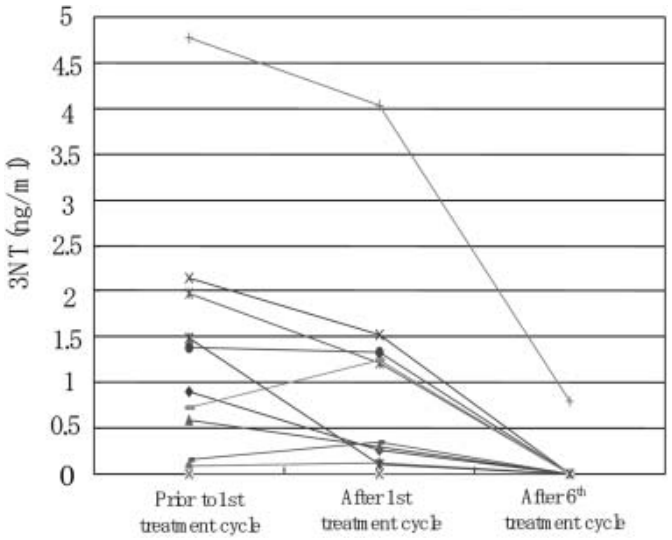


Fig 3. The number of spinal motor neurons in edaravone- and vehicle-treated wobbler mice. Mice treated with higher dose of edaravone increased the number of motor neurons significantly compared to vehicle. * $P<0.05$, the higher dose of edaravone group versus the vehicle group by one-way ANOVA and Dunnett multiple comparison test. Results are represented as the mean ± SEM ($n = 10$/group).

doi:10.1371/journal.pone.0140316.g003





The first, negative, trial (NCT00330681)

Post-hoc analysis (not preplanned)

Table II. Change in endpoints during treatment.

	Change in endpoints during treatment (ANCOVA)			
	Adjusted mean change LS Mean ± S.E.		Inter-group difference in adjusted mean change LS Mean ± S.E. (95% C.I.)	
	Placebo	Edaravone		p value
Primary endpoint				
ALSFRS-R	−6.35 ± 0.84 (99)	−5.70 ± 0.85 (100)	0.65 ± 0.78 (−0.90 – 2.19)	0.411
Secondary endpoint				
%FVC	−17.49 ± 2.39 (99)	−14.57 ± 2.41 (100)	2.92 ± 2.24 (−1.49, 7.33)	0.193
Grip strength	−5.71 ± 0.69 (99)	−4.81 ± 0.69 (100)	0.89 ± 0.64 (−0.37, 2.16)	0.165
Pinch strength	−1.03 ± 0.15 (99)	−0.83 ± 0.15 (100)	0.20 ± 0.14 −0.08, 0.48)	0.165
Modified Norris scale	−16.15 ± 2.00 (97)	−14.12 ± 2.05 (95)	2.03 ± 1.89 (−1.69, 5.75)	0.284
ALSAQ40	19.13 ± 3.79 (95)	19.60 ± 3.82 (95)	0.48 ± 3.50 (−6.44, 7.39)	0.892

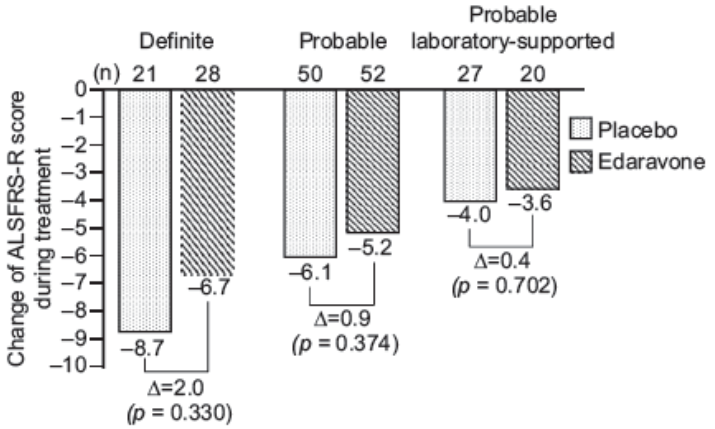


Figure 2. Change of ALSFRS-R score during treatment by diagnostic category. ALSFRS-R: the revised amyotrophic lateral sclerosis functional rating scale.

Table III. Adverse events and serious adverse events.

	AE				SAE			
	Placebo (104)		Edaravone (102)		Placebo (104)		Edaravone (102)	
Treatment	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Total	92	(88.5)	91	(89.2)	24	(23.1)	18	(17.6)
Constipation	17	(16.3)	13	(12.7)				
Dysphagia	12	(11.5)	8	(7.8)	11	(10.6)	8	(7.8)
Nasopharyngitis	22	(21.2)	22	(21.6)				
Muscular weakness	9	(8.7)	7	(6.9)	1	(1.0)	1	(1.0)
Contusion	5	(4.8)	12	(11.8)				
Headache	3	(2.9)	8	(7.8)				
Insomnia	10	(9.6)	9	(8.8)				
Gait disturbance	16	(15.4)	20	(19.6)	2	(1.9)	3	(2.9)
Eczema	2	(1.9)	7	(6.9)				
Glucose urine present	3	(2.9)	6	(5.9)				

All AE with an incidence greater than 5% are tabulated by the primary term, MedDRA version 11.1.

Abe et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients ALS 2014

The second, enriched, trial (NCT01492686)

Eligible patients were

1. aged 20–75 years.

2. independent living status (grade 1 or 2 in the Japan ALS Severity Classification).

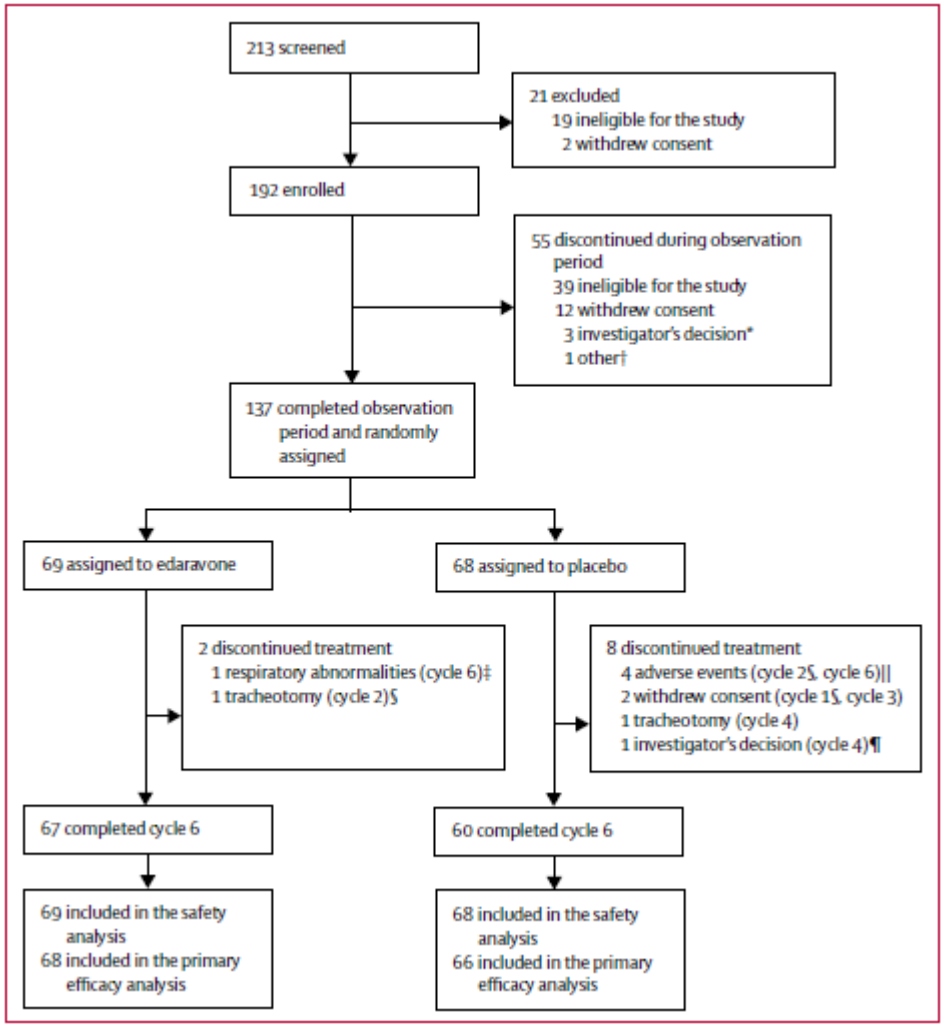
3. decrease in the ALSFRS-R score of 1–4 during a 12-week observation period.

4. eligible patients also had scores of at least 2 on all 12 items of ALSFRS-R.

5. FVC of at least 80%.

6. definite or probable ALS according to the El Escorial and revised Airlie House criteria.

7. duration of disease from the first symptom (any ALS symptom) of 2 years or less.



ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial Lancet Neurol 2017

Efficacy

- 2.5 points at ALSFRSr after six months (edaravone vs placebo)
- No significant difference in FVC and grip strength

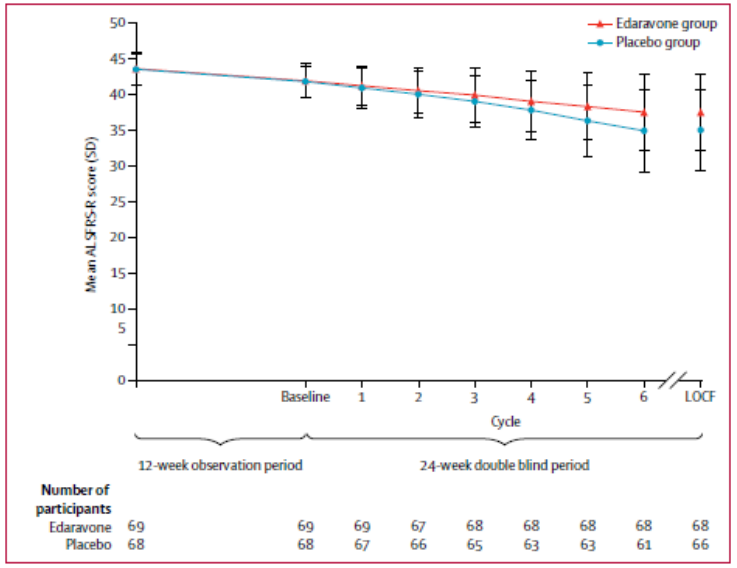


Figure 2: **Mean ALSFRS-R scores during treatment**
For patients with missing values at the end of cycle 6, data were imputed by the LOCF method, provided that they had completed at least cycle 3. ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. LOCF=last observation carried forward. One patient's evaluation at the end of cycle 2 was excluded from analysis as the clinician assessing ALSFRS-R score did not have adequate training.

	Adverse events		Serious adverse events	
	Edaravone group (n=69)	Placebo group (n=68)	Edaravone group (n=69)	Placebo group (n=68)
Any	58 (84%)	57 (84%)	11 (16%)	16 (24%)
Contusion	13 (19%)	9 (13%)	0	1 (2%)
Constipation	8 (12%)	8 (12%)	0	0
Dermatitis contact	8 (12%)	3 (4%)	0	0
Dysphagia	8 (12%)	10 (15%)	8 (12%)	8 (12%)
Eczema	5 (7%)	2 (3%)	0	0
Insomnia	5 (7%)	4 (6%)	0	0
Upper respiratory tract inflammation	5 (7%)	2 (3%)	0	0
Back pain	4 (6%)	1 (2%)	0	0
Headache	4 (6%)	5 (7%)	0	0
Myalgia	4 (6%)	1 (2%)	0	0
Nasopharyngitis	3 (4%)	5 (7%)	0	0
Respiratory disorder	3 (4%)	2 (3%)	2 (3%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	0	0
Speech disorder	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Pneumonia aspiration	0	2 (3%)	0	2 (3%)

Data are n (%). Includes all adverse events that had occurred in at least 5% of patients or were rated as serious adverse events in more than two patients in either treatment group during the specified study period. Adverse events were defined using the Medical Dictionary for Regulatory Activities, Japanese Version 17.0. Serious adverse events were defined as fatal, life-threatening, causing or potentially causing disability, or causing or prolonging hospitalisation.

Table 3: **Adverse events**

	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	−5·01, 0·64 (68)†	−7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013
Secondary endpoints				
FVC (%)	−15·61, 2·41 (67)†‡	−20·40, 2·48 (66)†	4·78, 2·84 (−0·83 to 10·40)	0·0942
Modified Norris Scale scores				
Total	−15·91, 1·97 (68)†	−20·80, 2·06 (63)†‡	4·89, 2·35 (0·24 to 9·54)	0·0393
Limb scale	−11·47, 1·61	−14·91, 1·68	3·44, 1·92 (−0·36 to 7·24)	0·0757
Bulbar scale	−4·44, 0·76	−5·89, 0·79	1·46, 0·90 (−0·33 to 3·24)	0·1092
ALSAQ-40 score	17·25, 3·39 (68)†	26·04, 3·53 (64)†‡	−8·79, 4·03 (−16·76 to −0·82)	0·0309
Grip strength (kg)§	−4·08, 0·54 (68)†	−4·19, 0·56 (66)†	0·11, 0·64 (−1·15 to 1·38)	0·8583
Pinch strength (kg)§	−0·78, 0·14 (68)†	−0·88, 0·14 (66)†	0·10, 0·16 (−0·23 to 0·42)	0·5478

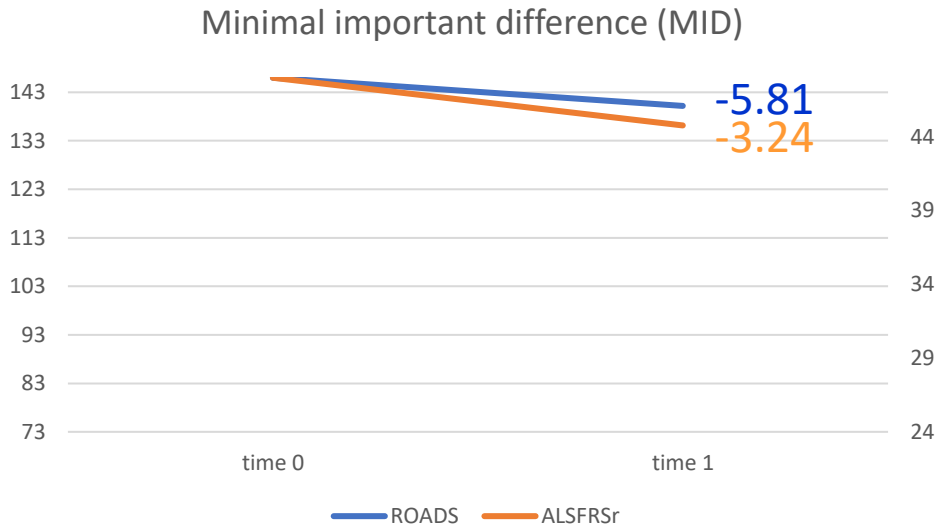
Data are least-squares mean change, SE (n); or least-squares mean difference, SE (95% CI). ALS=amyotrophic lateral sclerosis. ALSAQ-40=ALS Assessment Questionnaire. ALSFRS-R=Revised ALS Functional Rating Scale. FVC=forced vital capacity (%). LOCF=last observation carried forward. *Compared between treatment groups using an ANOVA with treatment group and three dynamic allocation factors. †The numbers of patients are different from full-analysis set, because for patients with missing values at the end of cycle 6, data were imputed by the last observation carried forward (LOCF) method, provided that they had completed at least cycle 3. In the analysis of the primary outcome, patients who did not reach the end of cycle 3 (1 in the edaravone group and 2 in the placebo group) were excluded from the full-analysis set (69 in edaravone group and 68 in placebo group). ‡The numbers of patients are different from full-analysis set, because of missing data (one FVC score in edaravone group, three Modified Norris Scale scores in placebo group, and two ALSAQ-40 scores in placebo group). §Mean for the left and right hands. ALSFRS-R scores 0–48 (best). Modified Norris Scale scores 0–102 (best). Modified Norris Scale scores (Limb scale) 0–63 (best). Modified Norris Scale scores (Bulbar scale) 0–39 (best). ALSAQ-40 score 200–40 (best).

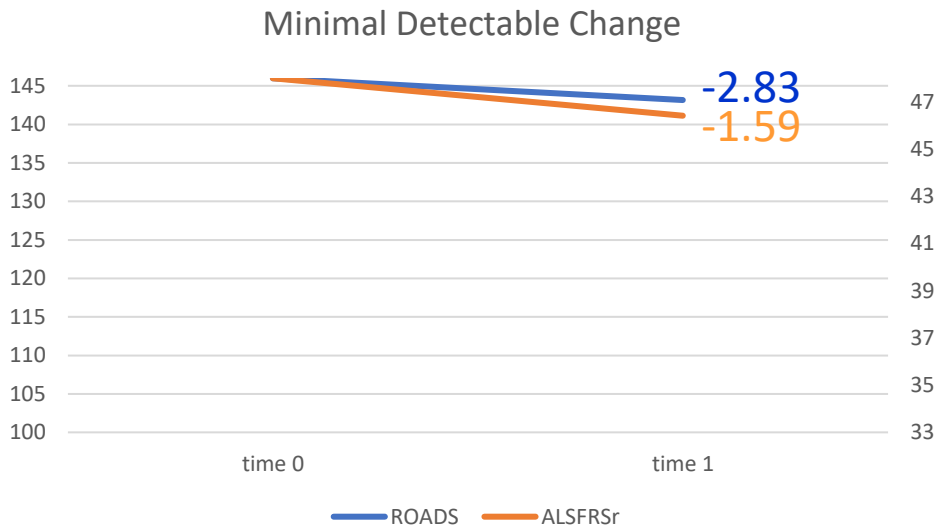
Table 2: **Primary and secondary endpoints**

ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial Lancet Neurol 2017

MCID - ROADS and ALSFRSr scales

- Minimal important difference (MID), or the smallest amount of change that is clinically relevant, was assessed based on patient reported impression of change for ROADS and ALSFRS-R.
- Minimal detectable change (MDC), the smallest amount of change exceeding the threshold for measurement error, was assessed for ROADS and ALSFRS-R using standard deviations for participants self-rated as “unchanged”
- Changes that are on average less than 5.81 points (3.98%) on the normed ROADS score or less than 3.24 points (6.75%) on the ALSFRS-R sum-score may not be clinically meaningful according to a patient-defined approach.





Fournier et al. Clinically meaningful change: evaluation of the Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) and the ALSFRS-R. ALS 2023

Journal of Neurology
https://doi.org/10.1007/s00415-020-09993-z

ORIGINAL COMMUNICATION

The Italian multicenter experience with edaravone in amyotrophic lateral sclerosis

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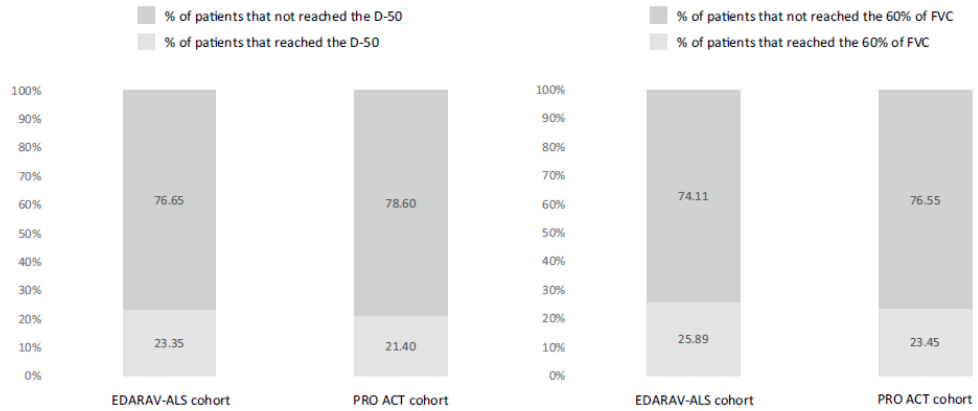
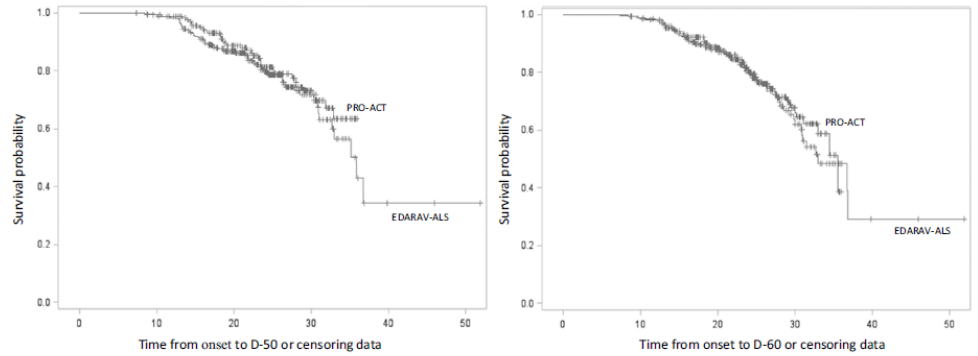
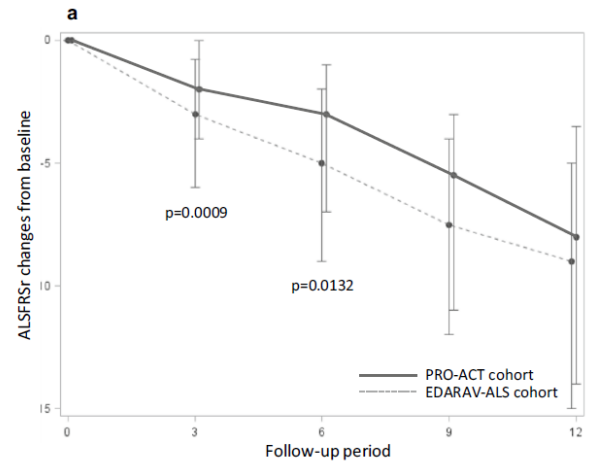
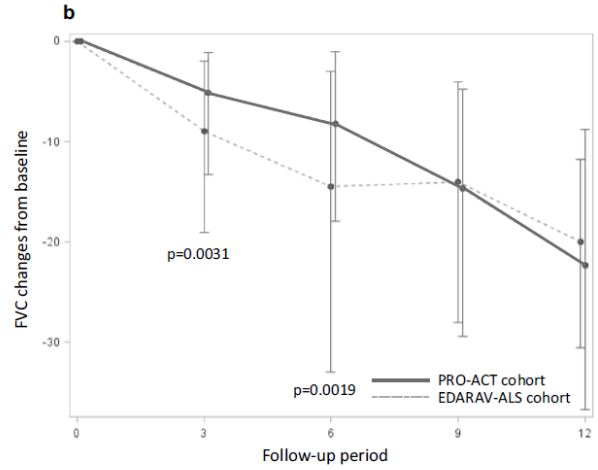


Fig. 2 Differences in proportions between the EDARAV-ALS and the PRO-ACT cohorts





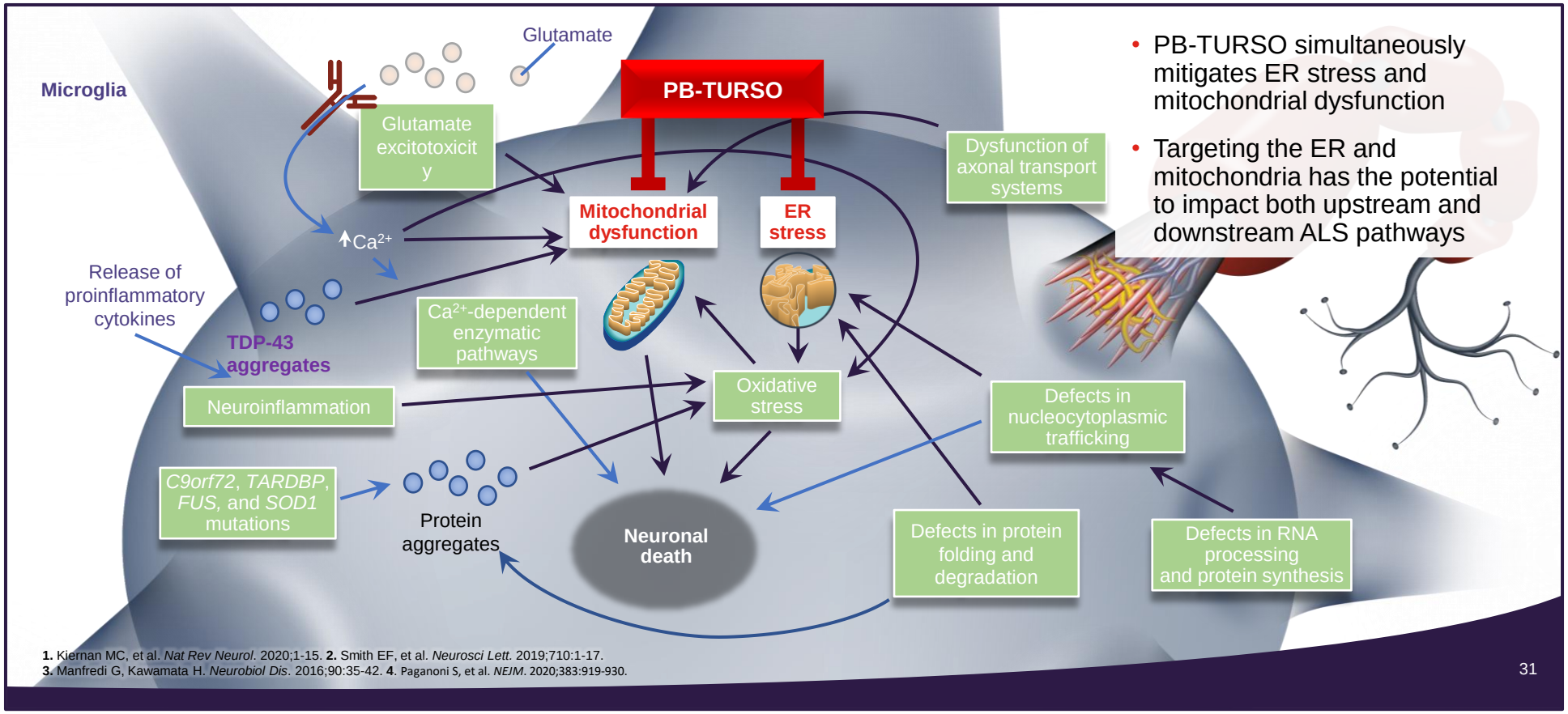
EDARAV-ALS cohort	N=197	N=184	N=128	N=74	N=53
PRO-ACT cohort	N=290	N=222	N=215	N=60	N=39



EDARAV-ALS cohort	N=197	N=173	N=122	N=67	N=44
PRO-ACT cohort	N=290	N=214	N=199	N=51	N=39

Phenylbutirrate + TURSO

PB-TURSO Targets Key Convergence Sites for Multiple Pathways Underlying ALS



Sodium phenilbutyrrate + TURSO

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Sodium Phenylbutyrate–Taurursodiol (N=87)	Placebo (N=48)	Overall (N=135)
Male sex — no. (%)	61 (70)	32 (67)	93 (69)
White race — no. (%)†	82 (94)	46 (96)	128 (95)
Age — yr	57.6±10.4	57.3±7.6	57.5±9.5
Bulbar onset — no. (%)	26 (30)	10 (21)	36 (27)
Riluzole or edaravone use — no. (%)‡	62 (71)	42 (88)	104 (77)
Riluzole	59 (68)	37 (77)	96 (71)
Edaravone	22 (25)	24 (50)	46 (34)
Both	19 (22)	19 (40)	38 (28)
Prebaseline ALSFRS-R slope§	0.95±0.43	0.93±0.60	0.94±0.49
Slow vital capacity — % of predicted normal value	83.6±18.2	83.9±15.9	83.7±17.4
ALSFRS-R total score§	35.7±5.8	36.7±5.1	36.0±5.5
Bulbar score	9.5±2.4	10.0±2.6	9.7±2.5
Fine-motor score	8.0±2.7	8.0±2.6	8.0±2.7
Gross-motor score	7.5±2.8	7.6±2.6	7.6±2.8
Breathing score	10.6±1.9	11.0±1.8	10.8±1.9
ATLIS upper-limb score — % of predicted normal value¶	54.8±24.4	51.4±25.2	53.6±24.6
ATLIS lower-limb score — % of predicted normal value¶	57.6±24.9	57.1±25.8	57.4±25.1
ATLIS total score — % of predicted normal value¶	56.8±20.1	53.9±20.9	55.8±20.4
Months since ALS symptom onset	13.5±3.8	13.6±3.6	13.5±3.8
Months since ALS diagnosis	5.9±3.3	6.3±3.2	6.0±3.3
Body-mass index‖	26.9±4.4	26.4±5.8	26.7±4.9

Entry criteria

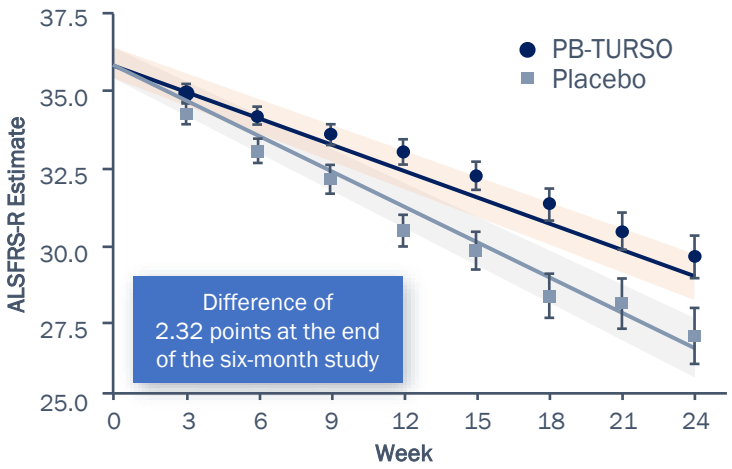
- Age >18 years
- Definite ALS
- <18 months disease duration
- SVC >60%

Paganoni et al. rial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis N Engl J Med 2020

The CENTAUR Trial results

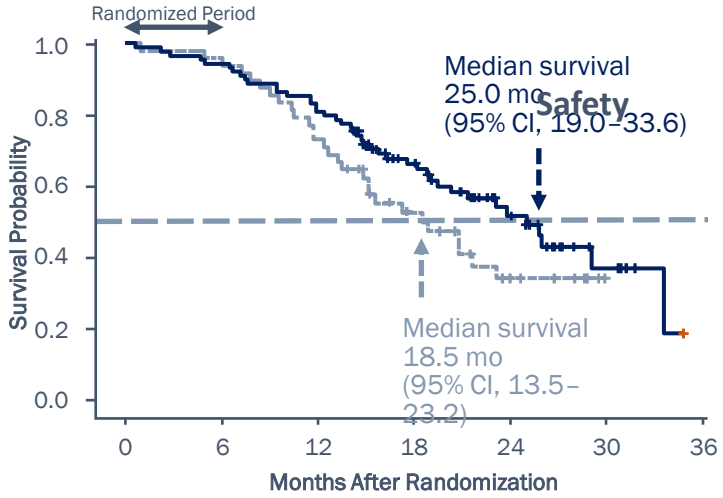
Function[1]

Primary Endpoint: ALSFRS-R Total



Survival[2]

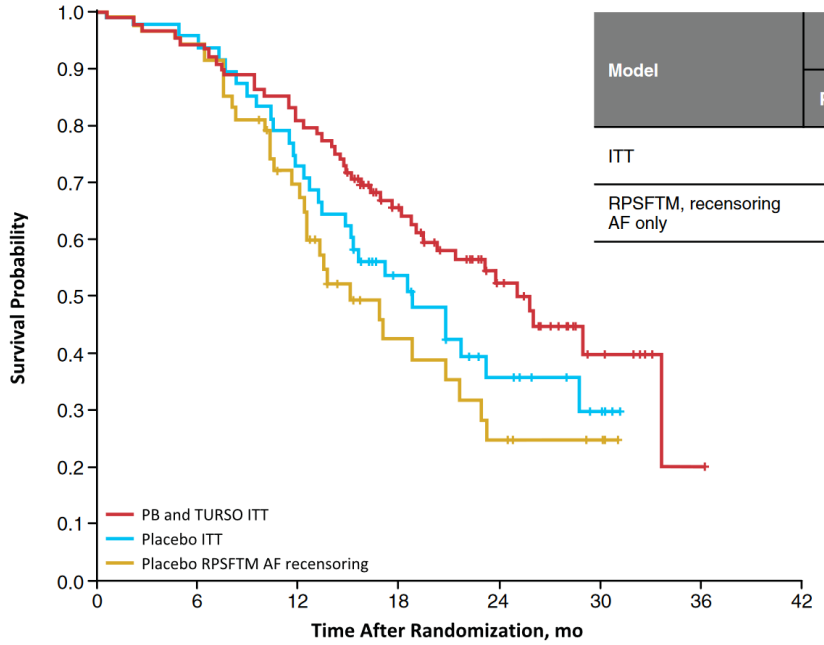
Pre-Specified Overall Survival Analysis



Adverse events with ≥5% incidence in either group — no. (%)†		
Gastrointestinal disorders	60 (67)	29 (60)
Musculoskeletal and connective-tissue disorders	38 (43)	21 (44)
Injury, poisoning, and procedural complications	35 (39)	23 (48)
Nervous-system disorders	33 (37)	19 (40)
Infections and infestations	28 (31)	21 (44)
Respiratory, thoracic, and mediastinal disorders	29 (33)	10 (21)
General disorders and administration-site conditions	20 (22)	13 (27)
Skin and subcutaneous-tissue disorders	16 (18)	8 (17)
Psychiatric disorders	14 (16)	9 (19)
Renal and urinary disorders	10 (11)	8 (17)
Metabolism and nutrition disorders	10 (11)	4 (8)
Cardiac disorders‡	7 (8)	0
Eye disorders	5 (6)	1 (2)

Paganoni S, et al. *NEJM*. 2020;383:919-930. Paganoni S, et al. *Muscle Nerve*. 2021;63:31-39.doi:10.1002/mus.27091. van den Berg LH, et al. Design of the international, randomized, placebo-controlled phase 3 PHOENIX trial of AMX0035 in amyotrophic lateral sclerosis. Abstract presented at ENCALS Virtual Meeting, May 12-14, 2021.

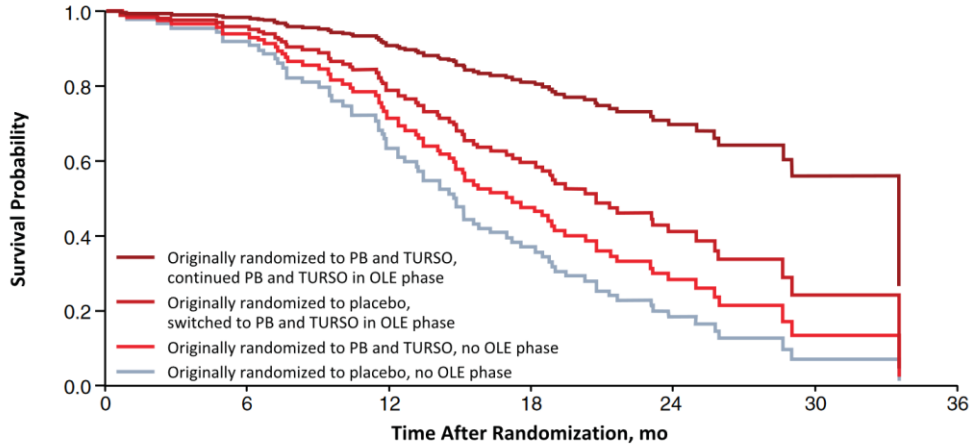
Centaur trial: analysis of survival by means of RPSFTMs (rank-preserving structural failure time models) analyses



Number at Risk								
PB and TURSO ITT	89	84	72	46	23	7	1	0
Placebo ITT	48	46	35	20	10	4	0	0
Placebo RPSFTM AF recensoring	48	45	29	12	7	3	0	0

Model	Median Survival Duration, mo		HR (95% CI)	*P* Value
	Placebo	PB and TURSO		
ITT	18.9	25.8	0.57 (0.35–0.92)	.023
RPSFTM, recensoring AF only	15.2	25.8	0.39 (0.17–0.88)	.023

Before RPSFTMs
+ 6.9 months
After RPSFTMs
+10.2 months



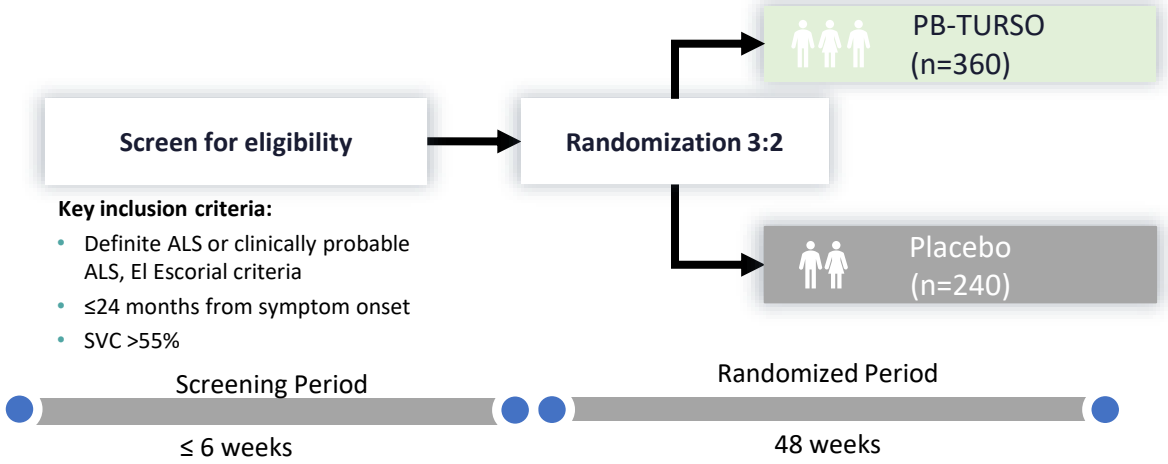
Subgroup		n	Mean PB and TURSO Exposure Duration, mo	Median (95% CI) Survival Duration, mo	HR (95% CI)[a]	*P* Value[a]
Randomized Phase	OLE Phase					
PB and TURSO	Yes	56	14.7	33.6 (28.7–NR)	NA	NA
Placebo	Yes	34	6.5	20.8 (16.3–NR)	2.48 (1.27–4.84)	.0077
PB and TURSO	No	33	2.7	17.0 (14.1–23.2)	3.54 (1.90–6.60)	<.0001
Placebo	No	14	0	14.8 (11.8–25.8)	4.78 (2.20–10.36)	<.0001

Paganoni et al. Survival analyses from the CENTAUR trial in amyotrophic lateral sclerosis: Evaluating the impact of treatment crossover on outcomes. Muscle and Nerve, 2022

PHOENIX Study Design

Primary Objectives

- To determine the **safety** and **tolerability** of PB-TURSO
- To measure the impact of PB-TURSO on **ALSFRS-R score** at 48 weeks with **joint assessment of function and survival**



Primary Efficacy Outcome

To measure the impact of PB-TURSO on ALSFRS-R score at 48 weeks with joint assessment of function and survival

Secondary Efficacy Outcomes

- SVC
- Patient reported outcomes (ALSAQ-40, EQ-5D, and EQ-VAS)
- Time to transition through King's and MiTos stages
- Time to death, tracheostomy, or PAV*

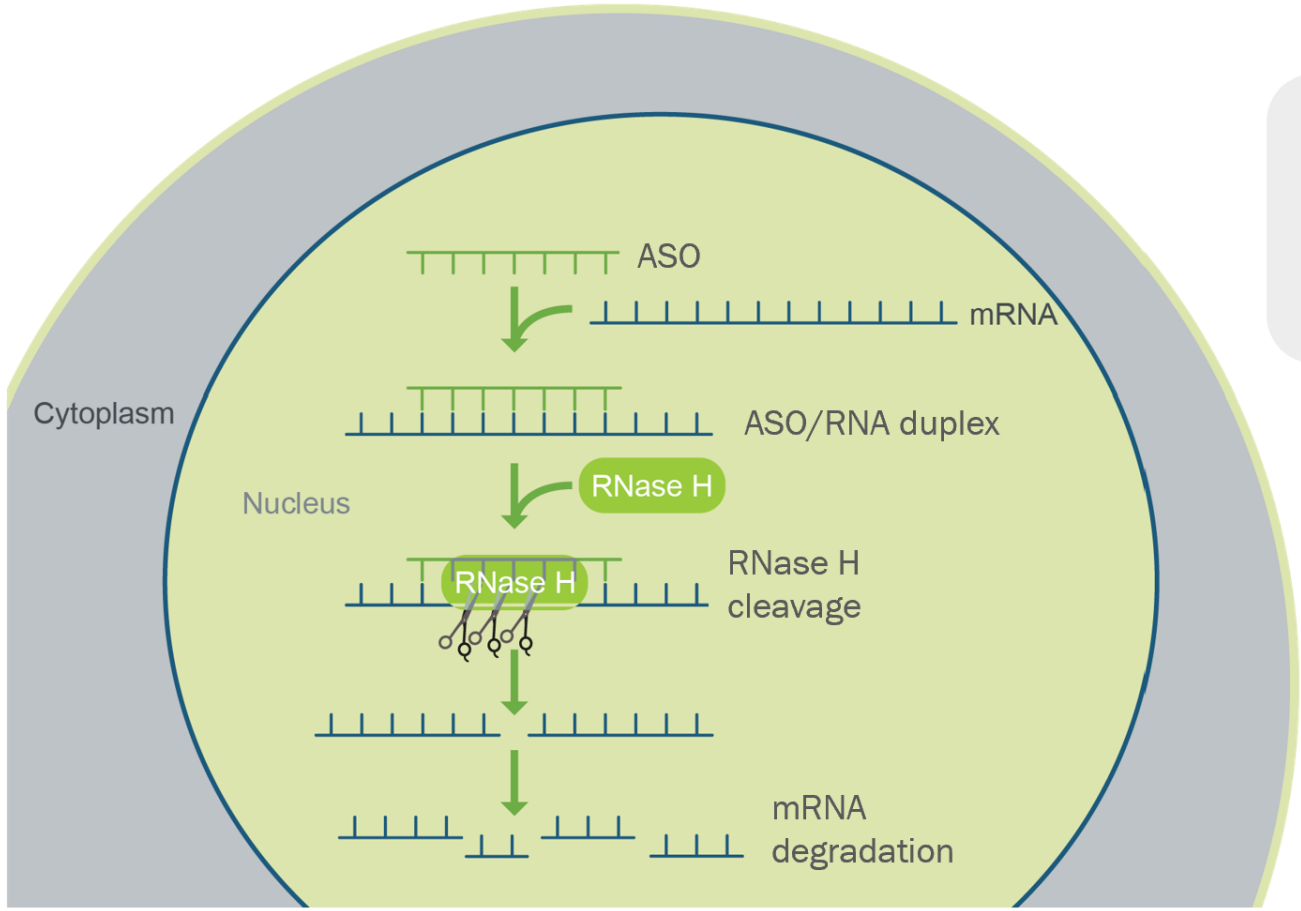
*PAV (>22 h/d for >7 days)

Long-term all-cause mortality will be assessed beyond the planned 48-week follow-up

ALSAQ-40, 40-item ALS Assessment Questionnaire; EQ-5D, EuroQol 5-Dimension; EQ-VAS, EuroQol Visual Analogue Scale; PAV, permanent assisted ventilation; SVC, slow vital capacity.

Tofersen

Tofersen* is a gapmer ASO that selectively targets SOD1 mRNA



Tofersen mediates RNase H-dependent degradation of *SOD1* mRNA to reduce the synthesis of SOD1 protein[1]

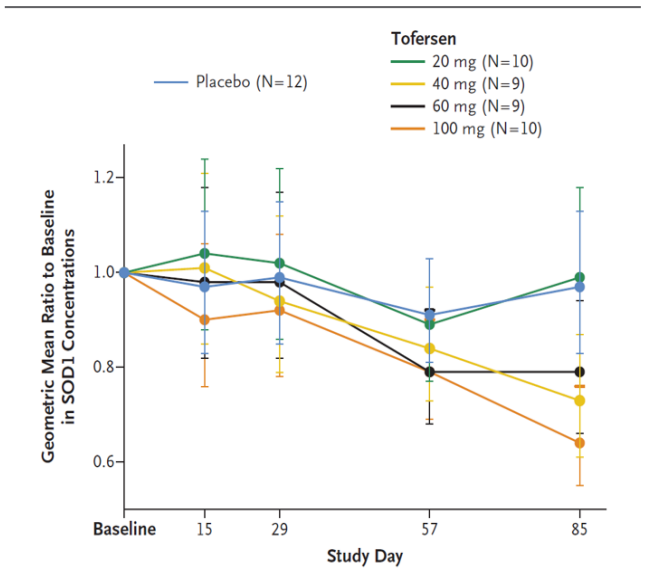
*Discovered by Ionis Pharmaceuticals

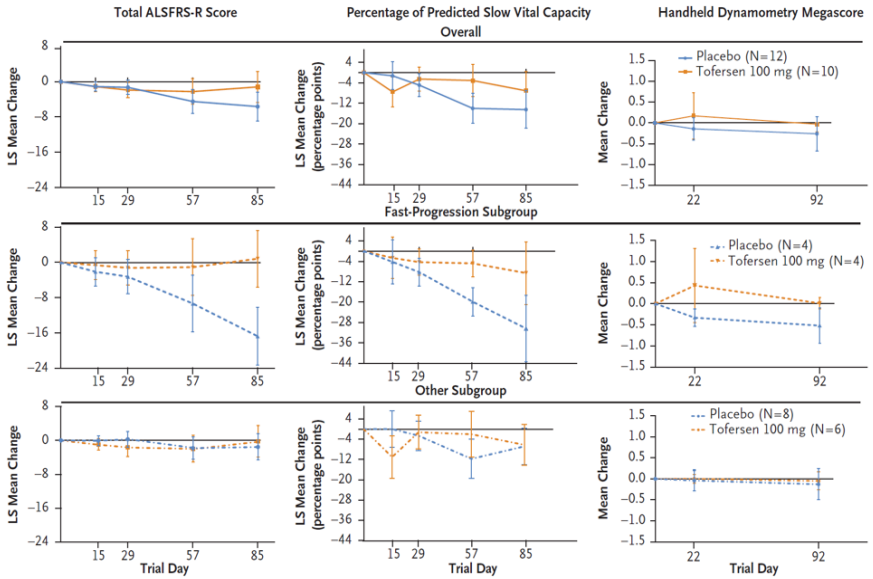
ASO, antisense oligonucleotide; mRNA, messenger RNA; RNase, ribonuclease; SOD1, superoxide dismutase 1.

1. Miller TM, et al. Lancet Neurol. 2013;12:435-42. Figure adapted from: Niemietz C, et al. Molecules. 2015;20:17944-75.

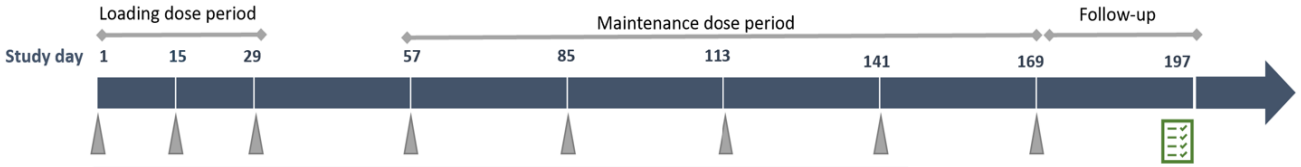
Tofersen: from phase ½ to phase 3

Phase 1/2





Phase 3



Treatment arms: tofersen 100 mg versus placebo, 15 ml intrathecal bolus over 1–3 minutes of treatment

Primary endpoint (efficacy)

- Change from baseline to Week 28 in the ALS-FRS-R total score

Key secondary endpoints (PD and efficacy)

- Change from baseline in total SOD1 and pNf-H concentration in CSF
- Change from baseline in SVC
- Overall and assisted-ventilation-free survival[a]
- Change from baseline in HHD

Miller et al. Phase 1-2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS . N Engl J Med 2020

VALOR study design[1,2]

ENDPOINTS

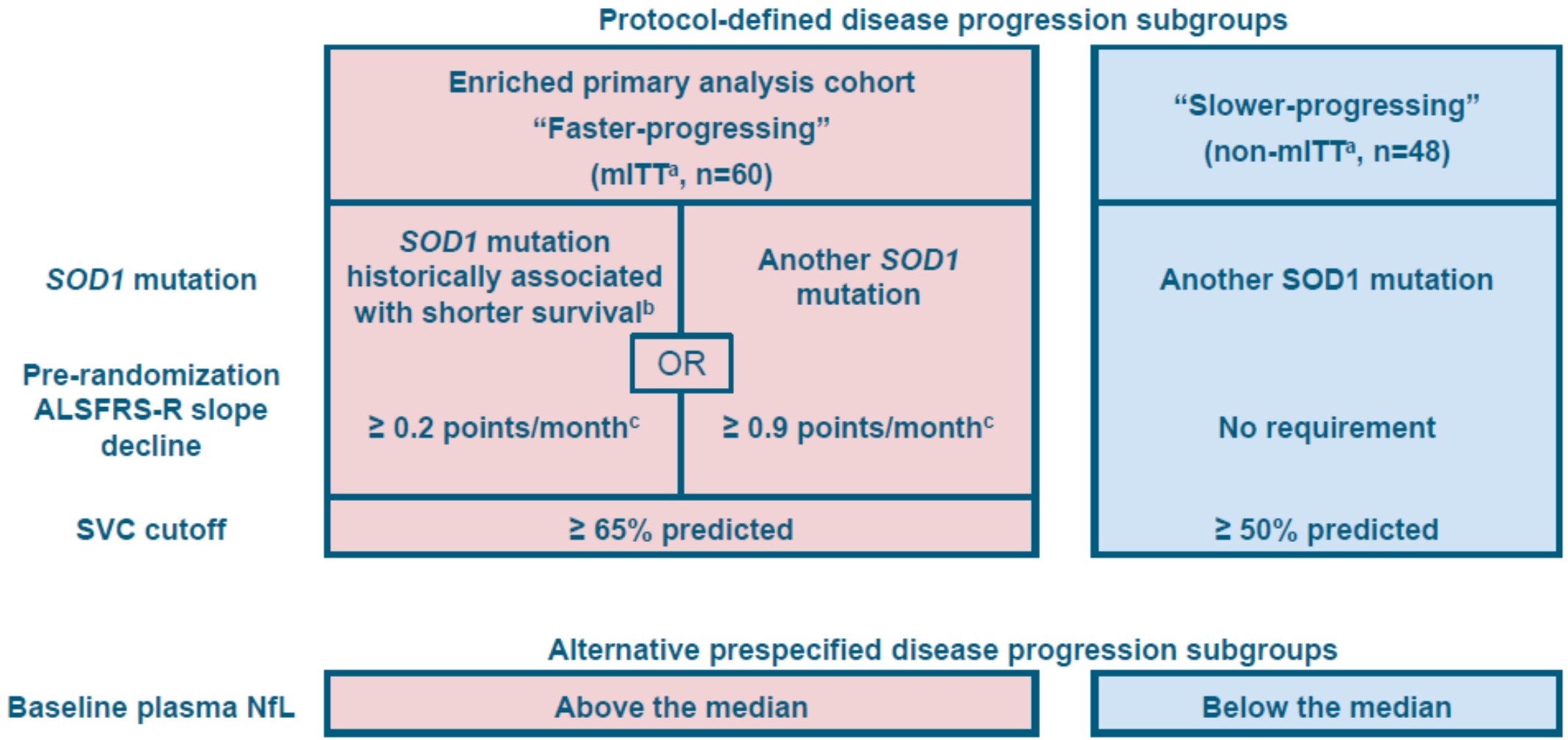
	Primary	Key Secondary	Key Exploratory
Clinical	ALSFRS-R total score	% predicted SVC HHD megascore Time to death or PV Time to death	
Fluid Biomarker		Total CSF SOD1 Plasma NfL	
Quality-of-life			ALSAQ-5

ALSAQ-5 = ALS Assessment Questionnaire; ALSFRS-R = ALS Functional Rating Scale–Revised; CSF = cerebrospinal fluid; HHD = handheld dynamometry; OLE = open-label extension; NfL = neurofilament light chain; PV = permanent ventilation; SVC = slow vital capacity

1. Biogen. Data on file. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02623699. Accessed August 1, 2021. 3. PV defined as ≥ 22 hours of mechanical ventilation (invasive or noninvasive) per day for ≥ 21 consecutive days.

Miller et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med 2022

Study enrichment



a. The study-defined modified intention to treat (mITT) population was the subset of this cohort that was randomized and received at least one dose of study treatment; all other participants comprise the non-mITT population; formal statistical testing of primary endpoint and key secondary endpoints (plasma NfL, SVC, HHD, time to death, time to death or permanent ventilation) performed in enriched primary analysis population (mITT) only
b. p.Ala5Val, p.Ala5Thr, p.Gly42Ser, p.His44Arg, p.Gly94Ala, p.Leu107Val, p.Leu39Val, p.Val149Gly, p.Leu85Val
c. Pre-randomization ALSFRS-R slope was calculated as [(48 – baseline score) / (time since symptom onset)].

Miller et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med 2022

Overview of safety

- Nearly all subjects had at least 1 TEAE; most events were mild-moderate in severity
- Many of the AEs were consistent with ALS disease progression or the LP procedure
- Most common events: procedural pain, headache, pain in extremity, back pain, and fall
- Overall safety profile in the OLE was comparable to VALOR
- Several participants treated with tofersen had SAEs involving the CNS
  - No similar events in the placebo group
  - Myelitis with sensory/motor deficits was clinically monitorable and reversible
- Many in the tofersen group had treatment-emergent CSF abnormalities; most of these were not reported as AEs

Serious neurologic events

Adverse event	VALOR		VALOR and OLE (Treated period)
	Placebo (N=36) n (%)	Tofersen 100 mg (N=72) n (%)	Tofersen 100 mg (N=104) n (%)
Subjects with serious neurologic events	0	4 (5.6)	5 (4.8)
Myelitis / Transverse myelitis	0	2 (2.8)	2 (2.0)
Meningitis chemical	0	1 (1.4)	1 (1.0)
Lumbar radiculopathy	0	1 (1.4)	1 (1.0)
Nervous system disorder	0	0	1 (1.0)

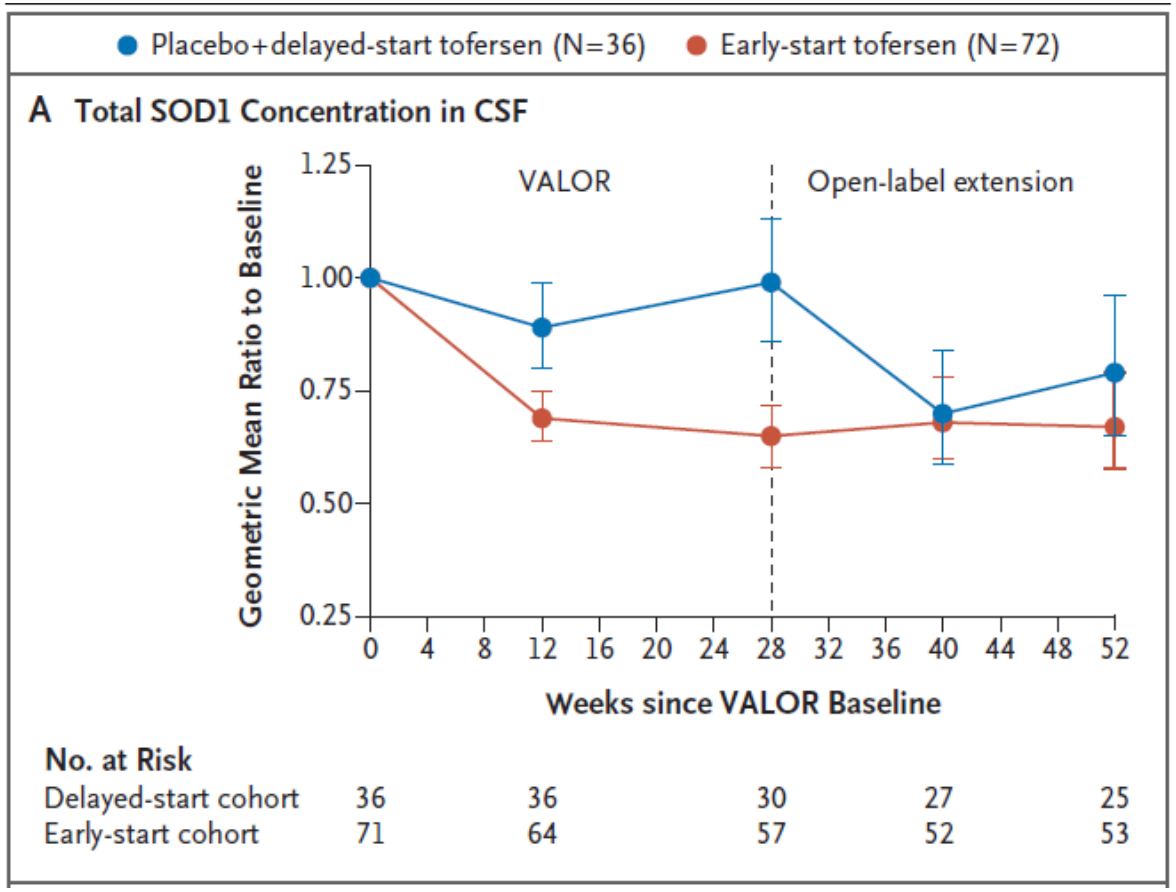
CSF parameter shift from baseline

CSF Shift to high leukocytes (10^6/L)	9/36 (25.0)	54/69 (78.3)	88/100 (88.0)
CSF Shift to high protein (mg/L)	6/20 (30.0)	31/46 (67.4)	54/68 (79.4)

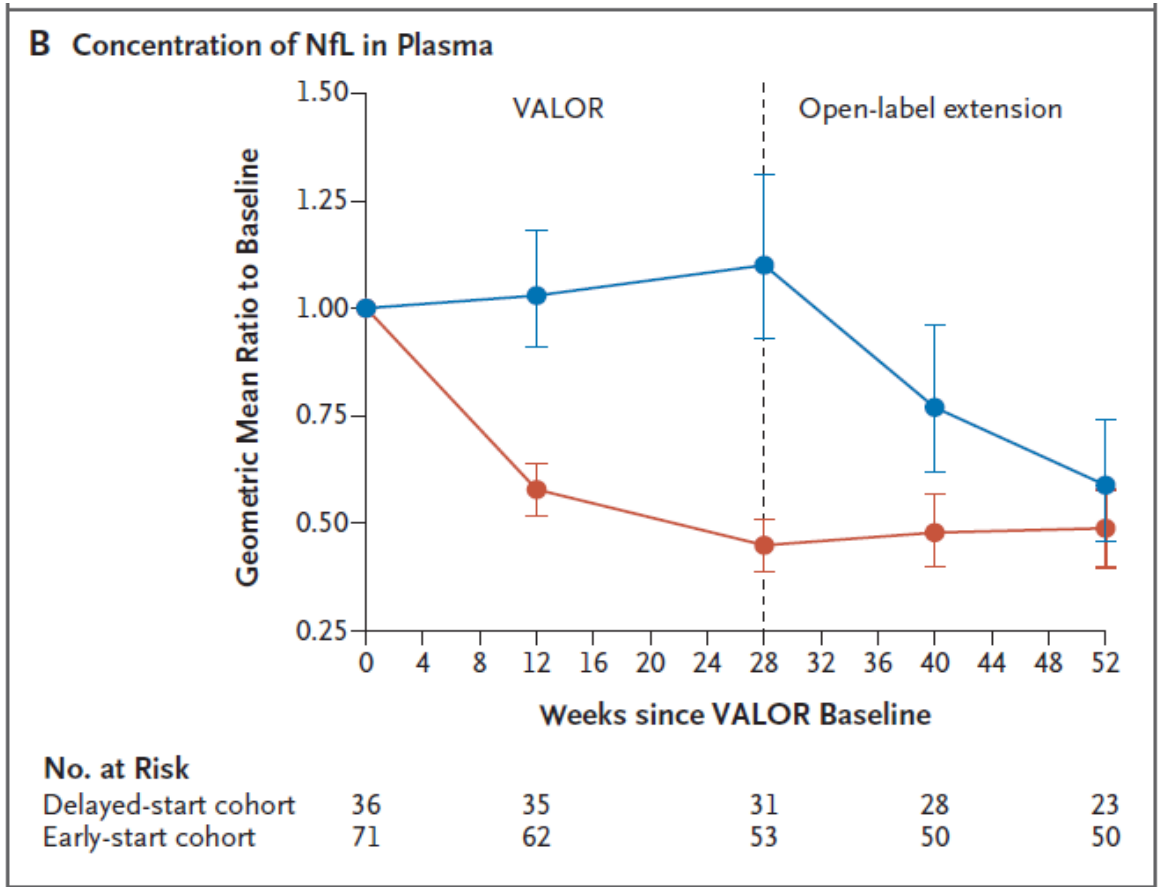
AE = adverse event; SAE = serious adverse event; TEAE = treatment emergent adverse event [23]

Miller et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med 2022

Results



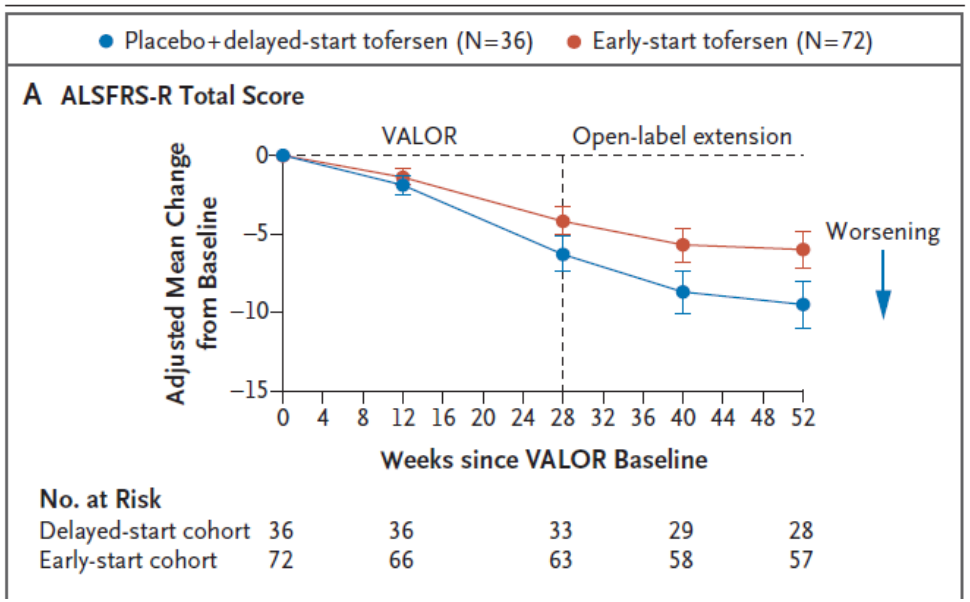
Target engagement

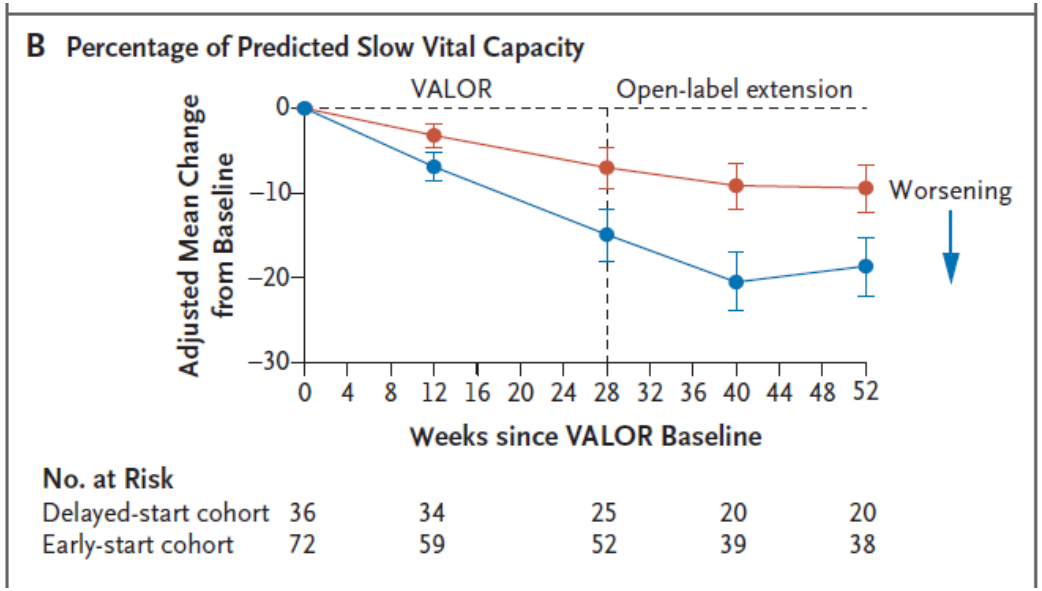


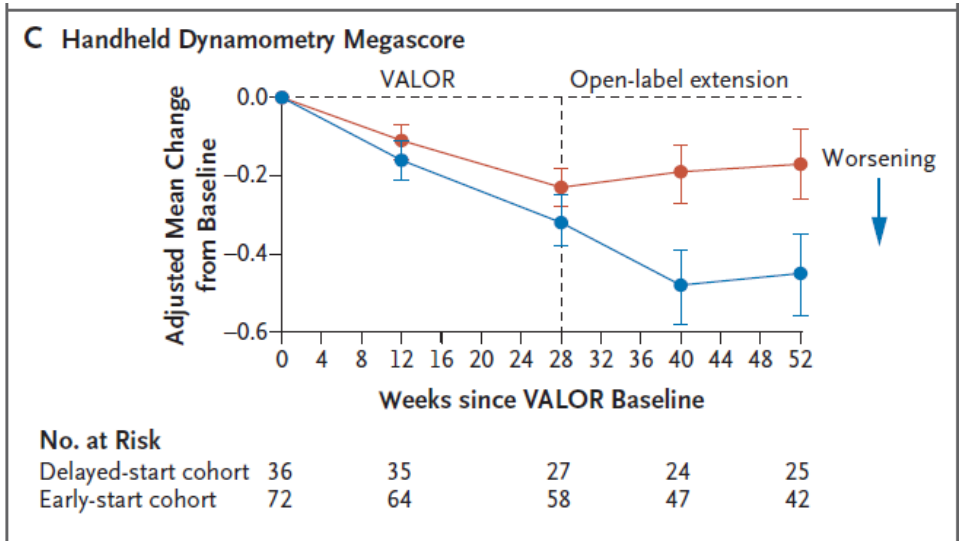
NfL, Biomarker of axonal damage

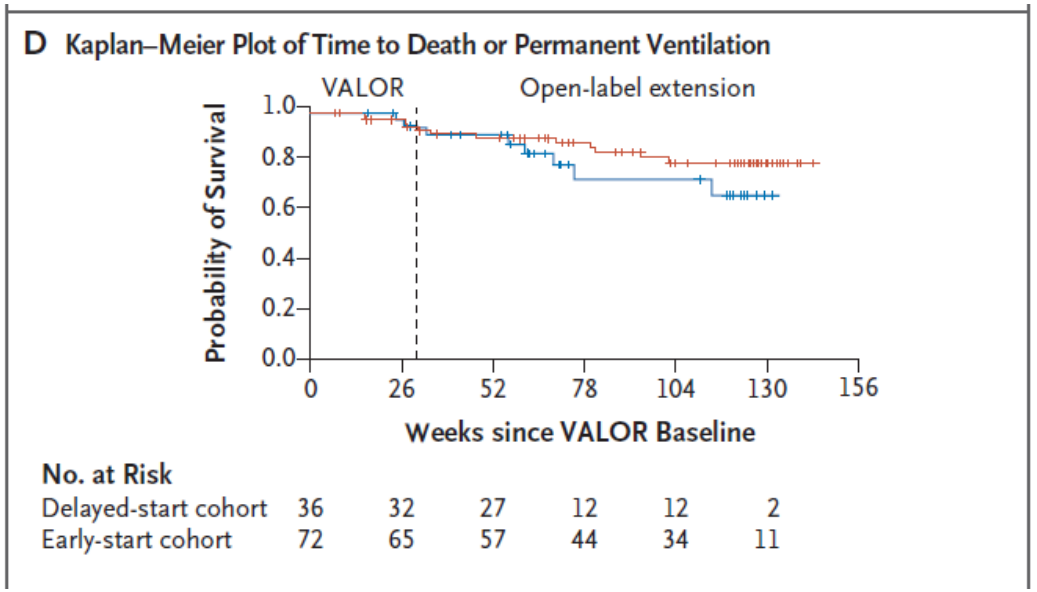
Miller et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med 2022

Results









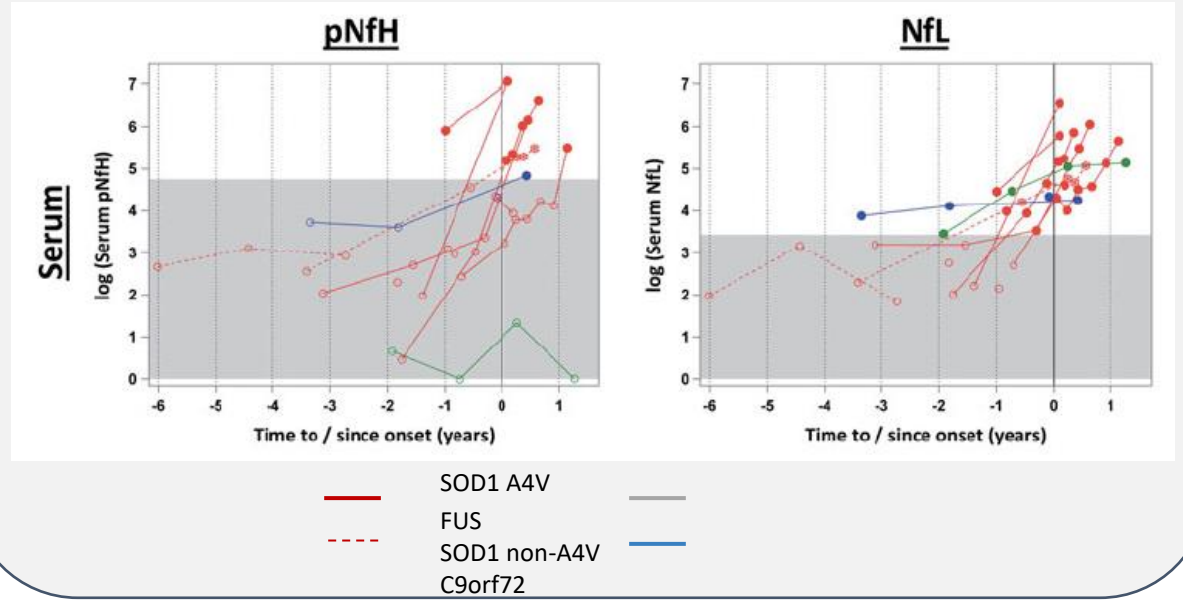
Miller et al. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALSN. Engl J Med 2022

Presymptomatic treatment of SOD1 carriers

Study objectives

ATLAS is being designed to evaluate whether tofersen, when initiated in presymptomatic carriers of rapidly progressive SOD1 mutations and biomarker evidence of disease, can delay clinical onset and/or slow the progression of disease

The study was designed in collaboration with Dr. Michael Benatar and informed by data from the University of Miami's Pre-FALS study [2,3]



New ALS therapies in the pharmacological armamentarium

- After more than 25 years, in USA 4 drugs registered for ALS are now available

- However, as always in medicine , this positive novelties carries new issues

The other side of the coin

- New challenges faces the clinicians, pwALS and their caregivers
  - What's the better drug for each pwALS?
  - Which is the better way to discuss with pwALS and their caregiver about the efficacy and side effects of available drugs?
  - Drug combination may prove additive effects?
  - What are the possible harms in combining drugs?
  - Will be drugs reimbursed by insurances to all patients or only to a subset of them?

NEWS · 30 MAY 2019

Tailored treatment for ALS poised to move ahead

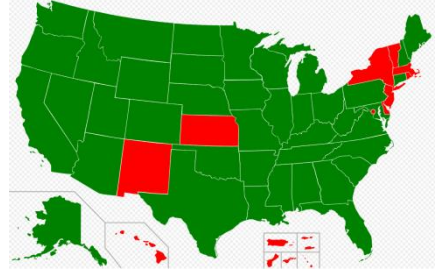
For a young woman with a rare disease, researchers are pushing the boundaries of personalized medicine

nature medicine

News of Mila's treatment broke just as 25-year-old Jaci Hermstad of Spencer, Iowa, began showing the first signs of amyotrophic lateral sclerosis (ALS). Jaci faced a disease with few therapies and no cures. Just as a custom-made ASO saved Mila, Jaci and her family hope that the same approach will help her. Together with Ionis Pharmaceuticals, neuroscientist Neil Shneider, director of the Eleanor and Lou Gehrig ALS Center at Columbia Medical Center, developed an ASO to target the FUS^{P525L} mutation that Jaci carries.

In late May, the US House of Representatives passed Jaci's Bill. The legislation, which was sponsored by embattled Congressman Steven King of Iowa and House Speaker Nancy Pelosi of California, urged the country's Food and Drug Administration (FDA) to allow Shneider to administer the ASO to Jaci before the completion of toxicology testing in rodents. It was an unusual bill in that it focused very narrowly on Jaci's access to the ASO. This week, the FDA formally signed off on the request.

Right-to-try



- **Right-to-try laws** are U.S. state and Federal laws that were created to let terminally ill patients try experimental therapies (drugs, biologics, devices) that have completed Phase I testing but have not been approved by the Food and Drug Administration (FDA). The value of these laws has been questioned on multiple grounds, including the fact that pharmaceutical manufacturers would have no obligation to provide the therapies being sought.

EXPERT OPINION

1. Introduction

Editorial

Should patients in need be given access to experimental drugs?

Arthur L Caplan† & Alison Bateman-House
†NYU Langone Medical Center, Division of Medical Ethics, New York, NY, USA

Dying patients want easier access to experimental drugs. Experts say that's bad medicine

29 March 2017, by Melissa Healy, Los Angeles Times

Right to Experimental Treatment: FDA New Drug Approval, Constitutional Rights, and the Public's Health

Elizabeth Weeks Leonard

Grazie per l'attenzione!

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