Review

# Review of disease-modifying drug trials in amyotrophic lateral sclerosis

Paolo Tornese [1], Stefania Lalli,[1] Antoniangela Cocco,[1] Alberto Albanese [1,2]

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[1]Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Italy
[2]Department of Neuroscience, Catholic University, Milan, Italy

**Correspondence to**
Professor Alberto Albanese, Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Italy; alberto.albanese@unicatt.it

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## ABSTRACT

We analysed clinical trials of pharmacological interventions on patients with amyotrophic lateral sclerosis (ALS), and compared study quality and design features. The systematic review included articles published in PubMed and trials registered in ClinicalTrials.gov. Included studies were randomised double-blind placebo-controlled clinical trials assessing a disease-modifying pharmacological intervention. Studies were excluded if primary end points were safety or dose finding. A total of 28 735 articles and 721 current trials were identified. 76 published articles and 23 ongoing trials met inclusion criteria; they referred to distinct populations comprising 22 817 participants with ALS. Most articles and all current trials had parallel group design; few articles had cross-over design. A run-in observation period was included in about 20% of published studies and ongoing trials. Primary end points included functional assessment, survival, muscle strength, respiratory function, biomarkers and composite measures. Most recent trials had only functional assessment and survival. Risk of bias was high in 23 articles, moderate in 35, low in 18. A disease modification effect was observed for 10 interventions in phase II studies, two of which were confirmed in phase III. Three confirmatory phase III studies are currently underway. The present review provides cues for the design of future trials. Functional decline and survival, as single or composite measures, stand as the reference end points. Post hoc analyses should not be performed, particularly in studies using composite end points. There is a general agreement on diagnostic criteria; but eligibility criteria must be improved. Run-in observations may be used for censoring patients but are discouraged for refining participants' eligibility. The ALS Functional Rating Scale-Revised needs improvement for use as an ordinal measure of functional decline.

Amyotrophic lateral sclerosis (ALS) is a fast-progressing deadly neurodegenerative disease for which there is no effective symptomatic treatment. The cause remains unknown for most of the patients, The average age of onset is between 58 and 60 years and the average survival from onset to death is 3–4 years.[1] The annual incidence is between 0.6 and 3.8 per 100 000 persons; but the prevalence is remarkably low, between 4.1 and 8.4 per 100 000 persons, due to the short life expectancy of affected individuals.[2] The incidence and prevalence of ALS are increasing in different parts of the world[2] and there have been repeated attempts to develop medications with a potential disease-modifying action.[3] Based on the results of successful trials, two compounds with such activity have received marketing authorisation for ALS: riluzole worldwide, and edaravone in a limited number of countries.[4]

Differently from other neurodegenerative diseases, ALS trials are minimally influenced by symptomatic treatments, have a relatively short duration, due to a rapid disease course and may adopt solid endpoints, such as measures of survival. This potential for new drug discovery conflicts with the scarcity of positive results of many trials. Biological, clinical and genetic heterogeneity of ALS are important factors influencing the outcome of clinical trials, suggesting that precision medicine paradigms will be required to realise effective therapy and improve the outcomes for individual patients with ALS.

Clinical trials are designed to consider key variables influencing outcome. Recommendations to improve the quality of ALS trial protocols have been proposed by expert panels and by regulatory agencies.[5–9] Different trial designs have been implemented over the last 40 years. A systematic review of pharmacological interventions for individuals with ALS may inform clinical practice and establish priorities for future studies.

## METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[10] The largest previous systematic reviews primarily studied end points in published trials[11] or explored research trends in current trials.[12] We developed search strings (comprising combinations of search terms, such as *amyotrophic lateral sclerosis*, *motor neuron disease* and *randomised controlled trial*) for PubMed, and ClinicalTrials.gov to identify relevant studies published or ongoing until March 2021. We subsequently reviewed the articles' references to help identify studies not populated by the search strings.

Studies were included in the review if (1) they were randomised double-blind placebo-controlled clinical trials, (2) they were assessments of a disease-modifying pharmacological intervention, (3) they had efficacy as primary end point, (4) they included human participants and (5) they were either published in a peer-reviewed journal in the English language or registered as current trials. Studies were excluded if primary end points were safety or dose finding, or if they assessed a symptomatic treatment. A single reviewer (PT) screened abstracts and titles. After the title and abstract screening, two independent reviewers (PT and AC) read the full articles of

**Table 1** Quality of published studies

| Study drug (trial number) * | Risk of bias | Inconsistency | Indirectness | Imprecision | GRADE rating | Funding |
|---|---|---|---|---|---|---|
| Brain gangliosides (Trial 1) | High | High | Moderate | High | Very Low | MDA |
| Cyclosporine (Trial 2) | Moderate | Low | Low | High | Low | MDA, Sandoz |
| Branched-chain aminoacids (Trial 3) | High | High | Moderate | High | Very Low | NIH |
| L-threonine (Trial 4) | Moderate | Low | Low | High | Moderate | Not available |
| Protropin (Trial 5) | High | Low | Moderate | Low | Low | MDA, Genentech, JDF; DoVA |
| Lamotrigine (Trial 6) | High | Low | Low | Low | Moderate | MRCC, ALS-BC |
| Branched-chain aminoacids (Trial 7) | Moderate | Low | Low | Moderate | High | Bracco |
| Physostigmine (Trial 8) | Moderate | Low | Low | High | Low | HF, ALS-SF |
| Deprenyl (Trial 9) | Low | Low | Low | High | Moderate | Not available |
| Riluzole (Trial 10) | Low | Low | Low | Low | High | Rhône-Poulenc Rorer |
| Acetylcysteine (Trial 11) | Low | Low | Low | Low | High | ALS-NLD, AMC-UvA |
| rhCNTF (Trial 12) | Low | Low | Moderate | Low | High | Syntex – Synergen |
| Nimodipine (Trial 13) | Moderate | Low | Moderate | Moderate | Low | Not available |
| Dextromethorphan (Trial 14) | Low | Low | Low | Moderate | Moderate | Not available |
| rhCNTF (Trial 15) | High | Low | Moderate | Low | Low | Regeneron |
| Riluzole (Trial 16) | Low | Low | Low | Low | High | Rhône-Poulenc Rorer |
| Branched-chain aminoacids – L-threonine (Trial 17) | Moderate | Low | Moderate | Low | Moderate | MDA, FDA, NIH |
| Gabapentin (Trial 18) | Moderate | Moderate | Moderate | Low | Moderate | Parke-Davis |
| Dextromethorphan (Trial 19) | Moderate | Moderate | Low | Moderate | Moderate | LHMF |
| rhIGF-I (Trial 20) | High | High | Low | Low | Low | Cephalon – Chiron, MDA |
| Selegiline (Trial 21) | Moderate | Moderate | Low | Moderate | Low | MDA |
| rhIGF-I (Trial 22) | High | Low | Low | Moderate | Moderate | Cephalon – Chiron |
| r-metHuBDNF (Trial 23) | Low | Low | Low | Low | High | Amgen |
| IFNβ–1a (Trial 24) | High | Low | Low | Low | Moderate | DFG |
| Vitamin E (Trial 25) | Moderate | Low | Low | Low | High | Rhône-Poulenc Rorer |
| Gabapentin (Trial 26) | Moderate | Moderate | Moderate | Low | Low | MDA, Warner-Lambert, FDA |
| Riluzole (Trial 27) | Moderate | Moderate | Low | Moderate | Low | Rhône-Poulenc Rorer |
| Creatine monohydrate (Trial 28) | Low | Low | Low | Moderate | High | ALS-DF, KNAW |
| Lamotrigine (Trial 29) | Moderate | Low | Low | Moderate | Moderate | Not available |
| Topiramate (Trial 30) | Moderate | High | Moderate | Low | Low | NINDS, MDA, McNeil, GCRC |
| Xaliproden (Trial 31) | Moderate | Moderate | Low | Low | Moderate | Sanofi – Synthelabo |
| Vitamin E (Trial 32) | High | Low | Low | Low | Moderate | CF |
| Creatine monohydrate (Trial 33) | Moderate | Low | Moderate | Low | Moderate | MDA, ALS-HF, Avicena |
| Indinavir (Trial 34) | Low | Low | Low | Low | High | ALSA, Merck |
| Pentoxifylline (Trial 35) | High | High | Low | Low | Low | ExonHit |
| Celecoxib (Trial 36) | Moderate | Low | Moderate | Low | Moderate | Pfizer—Pharmacia, MDA, GCRC |
| TCH346 (Trial 37) | Moderate | Low | Low | Low | Moderate | Novartis |
| Minocycline (Trial 38) | High | High | Low | Low | Low | NINDS, MDA |
| Creatine monohydrate (Trial 39) | Moderate | Low | Moderate | Low | Moderate | NIH, Avicena, GCRC |
| rhIGF-I (Trial 40) | Moderate | Low | Moderate | Low | Moderate | NIH, ALSA |
| CoQ10 (Trial 41) | Low | Low | Low | Low | High | NINDS, NIH |
| Valproic acid (Trial 42) | Low | Low | Low | Moderate | High | PBF |
| Glatiramer acetate (Trial 43) | High | Low | Low | Low | Moderate | Teva |
| G-CSF (Trial 44) | High | Low | Low | Moderate | Low | IMoJ, ISRALS |
| Lithium carbonate (Trial 45) | Low | Low | Low | Moderate | High | NINDS, ALSA, ALS-C |
| Talampanel (Trial 46) | Moderate | Low | Moderate | Low | Low | Not available |
| Memantine (Trial 47) | High | Low | Low | Low | Moderate | Lundbeck |
| Growth hormone (Trial 48) | Moderate | Low | High | Low | Very Low | AIFA, IMoH, Merk |
| Pioglitazone (Trial 49) | Low | Low | Low | Low | High | Takeda |
| Ursodeoxycholic acid (Trial 50) | High | Low | Low | Moderate | Low | SNUH |
| Lithium carbonate (Trial 51) | High | Low | Low | Moderate | Moderate | ZZF, ZF, ALS-NLD, OF, JCF |
| Acetyl-L-carnitine (Trial 52) | Moderate | Moderate | Low | Low | Moderate | AIFA, Sigma-Tau |
| Lithium carbonate (Trial 53) | Low | Low | Low | Low | High | MNDA |
| Dexpramipexole (Trial 54) | Moderate | Low | Low | Low | High | Biogen |
| Olesoxime (Trial 55) | Moderate | Moderate | Low | Low | High | Trophos, EU |
| Ceftriaxone (Trial 56) | Moderate | Low | Low | Moderate | High | NINDS |

Continued

**Table 1** Continued

| Study drug (trial number) * | Risk of bias | Inconsistency | Indirectness | Imprecision | GRADE rating | Funding |
|---|---|---|---|---|---|---|
| Edaravone (Trial 57) | Moderate | Low | Low | Low | High | Mitsubishi Tanabe |
| Erythropoietin (Trial 58) | Moderate | Moderate | Low | Low | High | IMoH |
| Tauroursodeoxycholic acid (Trial 59) | Moderate | Low | Low | Low | High | Bruschettini |
| Flecainide (Trial 60) | Moderate | Low | Low | Moderate | Moderate | NHMRC |
| Bromocriptine mesylate (Trial 61) | High | Low | Low | Moderate | Low | JMoH |
| Tiramsetiv (Trial 62) | High | Moderate | Low | Low | Low | Cytokinetics |
| Ozanezumab (Trial 63) | Moderate | High | Low | Low | Moderate | GlaxoSmithKline |
| Edaravone (Trial 64) | Moderate | Moderate | Low | Low | Moderate | Mitsubishi Tanabe |
| Edaravone (Trial 65) | High | Moderate | Low | High | Low | Mitsubishi Tanabe |
| Curcumin (Trial 66) | High | Low | Low | High | Low | Aliveda |
| Nanocurcumin (Trial 67) | Moderate | Low | Low | Low | Moderate | TUMS, Exir Nano |
| Rasagiline (Trial 68) | Low | Low | Low | Low | High | Teva |
| Rasagiline (Trial 69) | Low | Moderate | Low | Moderate | High | FDA, NCATS |
| Tiramsetiv (Trial 70) | High | Moderate | Moderate | Low | Low | ALSA, Cytokinetics |
| Methylcobalamin (Trial 71) | Moderate | Moderate | Low | Low | Moderate | Eisai |
| EH301 (Trial 72) | Moderate | Low | Low | High | Low | UCV, UV, Elysium Health |
| Levosimendan (Trial 73) | High | Low | Moderate | Moderate | Very Low | Orion |
| Tamoxifen (Trial 74) | High | Low | Low | High | Low | TMU |
| Sodium phenylbutyrate with tauroursodeoxycholic acid (Trial 75) | Low | Low | Low | Low | High | Amylyx, ALSFAC, ALSA |
| Masitinib (Trial 76) | Low | Low | Low | Low | High | AB Science |

*Trials are listed in online supplemental etable 3.
AIFA, Italian Medicines Agency; ALSA, ALS Association; ALS-BC, ALS Society of British Columbia; ALS-C, ALS Society of Canada; ALS-DF, ALS Dammers Fonds; ALS-HF, ALS Hope Foundation; ALS-NLD, Netherlands ALS Association; ALS-SF, ALS Super Fund; AMC-UvA, Academic Medical Centre, University of Amsterdam; ASFAC, ALS Finding a Cure Foundation; ASFAC, ALS Finding a Cure Foundation; CF, Charcot Foundation; CoQ10, coenzyme Q10; DFG, Deutsche Forschungsgemeinschaft; DoVA, US Department of Veteran Affairs; EU, European Union; FDA, Food and Drug Administration; GCRC, General Clinical Research CenterCentre; GCRC, General Clinical Research Centre; G-CSF, granulocyte-colony stimulating factor; HF, Hedco Foundation; IFNß–1a, interferon beta-1a; IMoH, Italian Ministry of Health; IMoJ, Israeli Ministry of Justice; JCF, Jan Cornelia Foundation; JDF, Joseph Drown Foundation; JMoH, Japanese Ministry of Health; KNAW, Royal Netherlands Academy of Arts and Sciences; KNAW, Royal Netherlands Academy of Arts and Sciences; LHMF, Louis Hansen Memorial Foundation; MDA, Muscular Dystrophy Association; MNDA, Motor Neuron Disease Association; MRCC, Medical Research Council of Canada; NCATS, National CenterCentre for Advancing Translational Sciences; NHMRC, National Health and Medical Research Council of Australia; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; OF, Optimix Foundation; PBF, Prinses Beatrix Fonds; rhCNTF, recombinant human ciliary neurotrophic factor; rhIGF-I, recombinant human insulin-like growth factor type I; r-metHuBDNF, recombinant human methionyl brain-derived neurotrophic factor; SNUH, Seoul National University Hospital; TMU, Taipei Medical University; TUMS, Tehran University of Medical Sciences; UCV, Catholic University San Vicente Martir; UV, University of Valencia; ZF, Zabawas Foundation; ZZF, Zeldzame Ziekten Fonds.

the remaining studies and completed a full-text review (details of the process are available in online supplemental efigure 1). Of the 416 studies read by the two reviewers, 99 studies met inclusion criteria.

Bias assessment of published studies was performed by two independent reviewers (PT and AC) using the Cochrane Risk of Bias for Randomized Trials, V.2, tool[13] (with risk of bias rated as low, some concerns or high based on five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result). The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[14] Disagreement between reviewers over study exclusion or inclusion and bias assessment was decided by discussion and consensus.

Data extracted included study type, run-in observation, study size, randomisation ratio, pharmacological intervention examined, duration of intervention, participant sex and age, number of participants in the treated and control groups, time from disease onset, primary end point and outcome assessment. The analysis identified three trial types (parallel-group, crossover or delayed start) and six primary end points of disease progression (functional decline, survival, loss of muscle strength, loss of respiratory function, markers of neuronal damage and quality of life questionnaires). Data were analysed from April to September 2021 using Excel software (Microsoft Corp).

## RESULTS

Our initial search identified 28 735 published articles and 721 current trials. After excluding duplicates, titles and abstracts were screened, and 416 studies were reviewed. A total of 76 published studies (48 phase II, 10 phase II/III and 18 phase III) and 23 current trials (nine phase II, 8 phase II/III and six phase III) were identified for inclusion (online supplemental efigure 1). The included trials were prevalently conducted in North America and Europe, had variable size and duration of treatment (online supplemental etable 1). The criteria used for diagnosis were relatively homogeneous among studies, whereas other eligibility criteria, such as disease duration, age, concomitant treatment, disease subtyping, familial occurrence and respiratory and swallowing functions greatly varied among studies (online supplemental etable 2). The included studies comprised 22 817 individual participants with ALS.

### Published trials

Most studies indicated an appreciable risk of bias, rated as moderate in 35, high in 23 and low in 18 (table 1). Forty-four studies were funded by pharmaceutical companies (16 of which cofunded by non-pharmaceutical sources), 26 studies were funded exclusively by non-pharmaceutical sources and 6 studies did not report funding. The GRADE score was high in 24 studies, moderate in 26, low in 22 and very low in 4. The quality

**Table 2** Design features of clinical trials reviewed

| Clinical trial features | Published trials (total=76) | Current trials (total=23) |
|---|---|---|
| *Trial type* | | |
| ► Parallel groups | 69 (90.8%) | 23 (100%) |
| ► Crossover | 6 (7.9%) | 0 |
| ► Delayed start | 1 (1.3%) | 0 |
| *Run-in observation* | | |
| ► No run-in observation | 61 (80.3%) | 18 (78.3%) |
| ► Refine patient eligibility | 10 (13.2%) | 4 (17.4%) |
| ► Assess baseline progression | 5 (6.6%) | 1 (4.3%) |
| *Endpoints* | | |
| ► Functional status (activities) | 28 (36.8%) | 15 (65.2%) |
| ► Survival | 16 (21.1%) | 1 (4.3%) |
| ► Muscle strength | 13 (17.1%) | 1 (4.3%) |
| ► Respiratory function | 2 (2,6%) | 0 |
| ► Neuronal damage | 1 (1.3%) | 0 |
| ► Composite measures | 16 (21.1%) | 6 (26.1%) |

of studies increased over time, as shown by a progressive reduction in the number of very low-quality studies and a progressive increase in the number of high-quality and moderate-quality studies.

Most trials (69 out of 76) had a parallel-group design, with subjects randomised to active or placebo arms and outcome measures compared between groups (table 2). The number of recruited patients varied from less than 10 to 474 in the active treatment arm. Duration of treatment also varied appreciably from 3 to 45 months (online supplemental etable 1). Six studies (on six different medications) implemented a cross-over design, which requires fewer patients to attain the same level of statistical power or precision of a parallel group. Consistently, cross-over trials had a smaller sample dimension (on average, 27 patients per group, from 5 to 59) and a shorter duration (from 14 days to 4 months per treatment segment) compared with parallel-group studies (online supplemental etable 1). Trial sequences had one (five trials) or two (one trial) switches and variable length. One trial had a delayed start design, with patients randomised to an early start group, receiving active medication for 6 months, or to a delayed start group, receiving placebo for the first 3 months and active medication for 3 more months.

Fifteen trials included a run-in observation period with repeated clinical assessments (table 2). In 10 studies on eight different medications, run-in served to determine participants' eligibility to continue in the trial. The main goals were to exclude patients with too fast or too slow progression trajectories or to stabilise concomitant medications before trial starts. Otherwise, in five trials, run-in observation served to provide a baseline measure of disease progression used to calculate trial outcome. In one such study, maximum voluntary isometric contraction during run-in served as the covariant component in the measure of muscle strength; in the other four studies, the revised ALS Functional Rating Scale (ALSFRS-R) slope was compared during run-in and at trial end.

Primary outcomes varied among published studies (table 3). Twenty-eight trials assessed functional decline as primary end point, measured by ALSFRS (1 study), ALSFRS-R (19 studies), Appel scale (five studies) or Norris scale (three studies). Sixteen studies had survival as primary end point, measured as time to death, non-invasive ventilation or tracheostomy. Thirteen trials instead measured loss of muscle strength, two trials measured loss of respiratory function and one measured markers of neuronal damage (table 3). Finally, 16 additional trials used combined primary end points, variably blending measures of functional decline, survival, muscle strength or respiratory function. Survival end points were treated as time-to-event measures in all studies; the other end points were treated as continuous measures in all but three studies that analysed functional decline data categorically. Two of those studies censored no longer self-sufficient patients; a third censored patients whose disease progression at trial end was reduced by at least 15% compared with run-in.

**Table 3** Primary outcomes in clinical trials reviewed

| Primary outcome measures | Published trials (total=76) | Current trials (total=23) |
|---|---|---|
| *Functional status (activities)* | | |
| ► ALSFRS | 1 | 0 |
| ► ALSFRS-R | 19 | 15 |
| ► Appel scale | 5 | 0 |
| ► Norris scale | 3 | |
| *Survival* | 16 | 1 |
| *Muscle strength* | | |
| ► Bulbar and spinal scores | 1 | 0 |
| ► Isometric strength | 1 | 0 |
| ► Manual muscle testing score | 1 | 0 |
| ► Maximal voluntary isometric contraction | 6 | 0 |
| ► Motor unit number index | 0 | 1 |
| ► MRC sum score | 4 | 0 |
| ► Tufts Quantitative Neuromuscular Evaluation | 3 | 0 |
| *Respiratory function* | | |
| ► Slow vital capacity | 2 | 0 |
| *Motor neuron function* | | |
| ► Magnetic resonance spectroscopy | 1 | 0 |
| *Composite measures* | | |
| ► ALSFRS-R+survival | 5 | 5 |
| ► ALSFRS-R+forced vital capacity | | 1 |
| ► Norris scale+survival | 2 | 0 |
| ► Norris+Appel scales+MRC sum score | 1 | 0 |
| ► Norris scale+Bulbar and spinal scores | 2 | 0 |
| ► Norris scale+grip strength+forced vital capacity | 1 | 0 |
| ► Survival+forced vital capacity | 3 | 0 |
| ► Neuromuscular+respiratory functional assessments | 1 | 0 |
| ► Maximal voluntary isometric contraction+forced vital capacity | 1 | 0 |

ALSFRS, ALS Functional Rating Scale; ALSFRS-R, ALS Functional Rating Scale-Revised; CBD, cannabidiol; CoQ10, coenzyme Q10; G-CSF, granulocyte-colony stimulating factor; IFNß–1a, interferon beta-1a; MRC, Medical Research Council; r-metHuBDNF, recombinant human methionyl brain-derived neurotrophic factor; rhCNTF, recombinant human ciliary neurotrophic factor; rhIGF-I, recombinant human insulin-like growth factor type.

## Trials with positive outcome

Eleven published trials (nine phase II, two phase III) had positive outcome, whereas 65 yielded negative results, either initially or after replication. Trials with positive outcome had different designs (table 4); their quality varied from very low to high.

**Table 4** Published clinical trials reporting ALS disease progression modification

| Study drug (Trial number) * | Phase | Run-in period | Trial type | Primary endpoint | Primary outcome | Data analysis | Phase III confirmed * |
|---|---|---|---|---|---|---|---|
| Riluzole (Trial 10) | II | None | Parallel group | Survival | Time to death or tracheostomy | Time-to-event | Yes |
| Riluzole (Trial 16) | III | None | Parallel group | Survival | Time to death or tracheostomy | Time-to-event | Yes |
| Acetyl-L-carnitine (Trial 52) | II | None | Parallel group | Functional decline | ALSFRS-R | Categorical | No |
| Tauroursodeoxycholic acid (Trial 59) | II | Baseline progression | Parallel group | Functional decline | ALSFRS-R | Categorical | Ongoing |
| Edaravone (Trial 64) | III | Patient eligibility | Parallel group | Functional decline | ALSFRS-R | Continuous | Yes |
| Curcumin (Trial 66) | II | None | Delayed start | Functional decline | ALSFRS-R | Continuous | No |
| Nanocurcumin (Trial 67) | II | None | Parallel group | Survival | Time to death or mechanical ventilation | Time-to-event | No |
| EH301 (Trial 72) | II | None | Parallel group | Functional decline | ALSFRS-R | Continuous | No |
| Levosimendan (Trial 73) | II | None | Crossover | Loss of respiratory function | Vital capacity | Continuous | No |
| Sodium phenylbutyrate with tauroursodeoxycholic acid (Trial 75) | II | None | Parallel group | Functional decline | ALSFRS-R | Continuous | Planned |
| Masitinib (Trial 76) | II | None | Parallel group | Functional decline | ALSFRS-R | Continuous | Ongoing |

*Trials are referenced in online supplemental etable 3.
ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic lateral sclerosis functional rating scale-revised.

A disease-modifying action of riluzole is supported by two controlled trials with parallel-group design. A first phase II trial had survival and functional decline as coprimary end points,[15] but only survival showed efficacy. A second phase III trial, using tracheostomy-free survival as single time-to-event end point, was also positive.[16] A third phase III trial assessing patients with advanced disease stages failed to replicate the observation.[17] Quality of evidence was high for the two successful trials, low for the third one (table 1).

Following a first phase III negative trial on edaravone,[18] post hoc analysis of the same data suggested a potential benefit in patients with scores ≥2 on all ALSFRS-R items, forced vital capacity at baseline of at least 80% and disease duration ≤2 years. This subpopulation represented only 24% of the originally included Japanese patients. The same post hoc criteria became the inclusion strategy of a 6-month phase III prospective trial confirming a 2.5 ALSFRS-R score difference favouring edavarone over placebo.[19] This study included a 12-week run-in period to select this specific patient subpopulation. The primary end point was functional decline, measured by ALSFRS-R as continuous variable. A third study by the same research group, with similar design, including patients with slightly more severe disease at inclusion, showed no efficacy.[20] The quality of evidence was high for the first negative trial, moderate for the second positive trial and low for the third negative trial (table 1).

Eight additional medicinal products were positively tested in phase II trials (table 4). Tauroursodeoxycholic acid and masitinib are currently under phase III assessment (NCT03800524 and NCT03127267); a phase III study is planned for the combination of sodium phenylbutyrate with tauroursodeoxycholic acid (NCT05021536). Quality of evidence is high for the three original phase II studies. No confirmatory phase III studies are planned for the other five phase II trials, whose quality of evidence was moderate (acetyl-L-carnitine and nanocurcumin), low (curcumin and EH301) or very low (levosimendan) (table 1).

## Current trials

All current trials have a parallel group design, with variable sample sizes (from 15 to 265 patients per treatment arm) and different durations (from 4 to 19 months) (online supplemental etable 1). There is heterogeneity in eligibility criteria (online supplemental etable 2). In four trials, run-in observation harmonises patient inclusion criteria before trial. In another study, run-in observation censors individual patient response comparing ALSFRS-R slopes before and after the experimental treatment.

In 15 trials, primary end point is functional decline measured by ALSFRS-R, in one is survival, and in one is loss of muscle strength, measured by decline in the motor unit number index (table 3). Six other trials use combined end points: survival and ALSFRS-R (five studies) or forced vital capacity and ALSFRS-R (one study). Survival is treated as time-to-event measure; the other end points are treated as continuous measures in 21 studies. One trial has categorical data analysis based on censoring individual disease progression respect to a predefined threshold.

## DISCUSSION

The current systematic review identified a small number of positive studies of pharmacological interventions for patients with ALS. Two drugs whose efficacy was confirmed in phase III trials have been approved as disease modifiers and three phase III trials are currently underway on compounds with positive phase II outcomes. Despite several pharmacological trials and the involvement of more than 22 000 participants, few have

so far provided evidence for disease modification. The review evidenced not only a trend to standardise ALS diagnostic criteria but also differences remaining for other key eligibility criteria. In most studies, ALS diagnosis conformed to the World Federation of Neurology El Escorial criteria[21] (online supplemental etable 2) notwithstanding the introduction of more recent proposals.[22 23] On the other hand, the review reports inconsistent adoption of other eligibility criteria, such as disease duration from symptoms onset, concomitant therapy, respiration and swallowing functions and the genetic status. Primary end points and outcome measures have progressively crystallised to three choices: functional status assessed by ALSFRS-R, survival and muscle strength assessed by motor unit number index. There were two main study designs, parallel groups and crossover, with addition of a run-in observation in 20% of trials. Trial quality improved over time, as shown by increase in moderate and high-quality studies and decrease in very low-quality studies. Most high-quality published studies and all current trials have parallel group design. Higher quality phase II studies with positive outcome were more likely to be replicated by phase III clinical trials.

Fifteen published and five current trials added a run-in observation period. This design type delays the experimental treatment by some months and may potentially result in lower recruitment rates and increased dropouts of patients with more rapid disease progression.[24] The reasons for including run-in observations were twofold: to determine participants' eligibility to continue in the trial or to establish baseline measurements for comparison after the intervention has been applied. Adding a run-in period may introduce various forms of bias.[25] Run-in refining participants' eligibility enhances selection of participants at the cost of potentially reducing generalisability of results and should be interpreted with caution.[25] This design was found in 14 published studies, including one trial with positive outcome and ensuing regulatory approval.[19] Generalisability plays a central role in the translation of trial results to medical decision-making.[26] It has been reported that at least 59.8% of patients with ALS are excluded from participation in clinical studies.[27] Clinical trials with highly selected subgroups are difficult to interpret in real-world settings, and the safety or effectiveness of a drug may be unknown for many patients. Eligibility criteria shape the prognosis of participating patients,[28] impact on their possibility to complete the study[29] and influence the generalisability of results. A consensus on eligibility criteria taking into account clinical, genetic and biomarker indicators may improve the design of future studies by assembling well-defined patient cohorts.[27]

The symptoms of ALS were assessed using a variety of outcome measures. Functional decline and survival were the most adopted primary outcomes; on the other hand, loss of muscle strength and respiratory function were the least used (table 3). Survival is a robust measure for inevitably fatal diseases.[30] There was a progressive decrease in the number of studies measuring survival as single primary end point, counterbalanced by an increased usage of composite end points that include survival as component (22% of current trials). The definition of time to death or to a clinically significant event introduces variability, particularly in multicentre studies, since life-extending respiratory interventions are not applied uniformly and it remains impossible to control all factors that influence mortality of patients with ALS, such as nutrition, respiratory assistance or caregiver support.[31] Furthermore, an adequate trial length is needed to detect differences in survival[32] and studies measuring survival were on average longer than those measuring functional decline (a median of 18 months compared with 8.5 months; online supplemental etable 2; 3). Therefore, a joint model may circumvent the pitfalls encountered by individual end points.[33] The purported benefits of combining these two measures include increased statistical efficiency, decrease in sample-size requirements, shorter trial duration and decreased cost. The Combined Assessment of Survival and Function is a predefined composite score analysing the ALSFRS-R and survival components.[34] There are, however, limits to this evolution: composite end points increase false-negative rates,[33] the use of non-parametric rank analysis limits direct comparability of end point measures across trials,[35] and clinimetric studies validating the composite measures are not available yet. The limitations inherent to the ALSFRS-R also influence composite end points, and post hoc analysis may become necessary to reconstruct the single score effects.[36] Survival and ALSFRS-R scores are independently interrelated[37] and it remains to specifically assess whether and to what extent combining these two measures provide a basis for medical decision-making.[38] While symptom progression influences both functional decline and survival, these two end points are differently impacted by the possibility that a patient completes the study. Considering the average duration of a clinical trial, patients with faster progression likely reach the survival threshold during the study, whereas those with slower progression may reach the same threshold after trial end and miss the study end point (figure 1). Functional decline captures progression in all patients during the trial, but data will be missing for those who do not survive until the end of study. Identifying markers that define homogeneous patient cohorts would facilitate the objectification of a treatment effect in defined small patient groups. The review highlights the enrolment dilemma for a disease like ALS, where enrolling a subset of participants boosts statistical power but threatens generalisability, and enrolling a broadly representative population improves generalisability but reduces statistical power. Phenotypic and genetic heterogeneity of ALS have

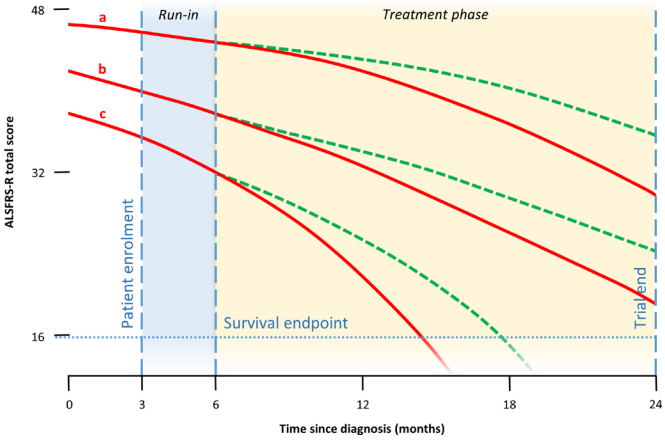


**Figure 1** Interrelationship between functional decline (measured by ALSFRS-R score) and survival during a clinical study. Longitudinal ALSFRS-R patterns are extracted from the natural progression reported in a pooled population of ALS patients.[27] Plots correspond to the upper border of aggregated patterns (a, milder progression), the average rate of decline (b),and the lower border of aggregated patterns (c, more severe progression). These representative patients are assumed to start the clinical trial treatment phase 6 months after diagnosis. The natural progression pattern is shown in red; green plots show a 25% disease modification effect in the treatment arm. Patients with milder progression (a, b) complete the 18-month trial without meeting the survival endpoint; patients with a more severe course (c) meet the survival endpoint during the trial and drop-out during the treatment phase.

been documented, but it is not demonstrated how they would influence the conduct of clinical trials.[39] Conversely, variables inherent to clinical trial design directly influence trial outcome.[29]

ALSFRS-R is the most widely used clinical measure of functional decline in ALS trials that reliably predicts disease progression and survival.[40 41] Despite this proven strength, the total ALSFRS-R score has been considered not to adequately account for the variability of disease[42] and not to encompass some clinically relevant domains, such as cognitive function,[43] pain[44] and quality of life.[43–45] The clinimetric properties also suggest a non-linear scale response across disease course[46] and a reduced sensitivity to detect functional changes, particularly in patients with lower scores.[47] Assessment of functional decline may be biased when using linear estimates of progression. Furthermore, ALS has a curvilinear natural progression trajectory, with a faster rate of decline at the first and latest phases of the disease and a slower rate of progression during the central stage.[48] The shape of progression trajectories varies among patients.[46] The total ALSFRS-R score range is narrow (from 0 to 48) compared with other clinical rating tools. Older ALS functional rating tools had wider score ranges: the Norris scale varied from 0 to 120,[49] the Appel scale from 30 to 164.[50] Clinical rating scale scores are technically ordinal data that can be approximate to continuous variables when they comprise relatively wide ranges of possible scores.[51] It is, therefore, hazardous to use Likert conversions or to restrict analysis to a subscale. Due to its narrow range, the total ALSFRS-R score is also subjected to additional bias generated by missing data, due to dropouts or deaths during the trial.[35 52] There are, therefore, implicit limitations when using the ALSFRS-R as a continuous measure, which do not occur in studies that measured individual baseline ALSFRS-R progression before treatment and censored patients according to changes in disease progression trajectory after treatment. This design type is in keeping with recent recommendations that suggest identifying patient with ALS subgroups who do respond to a treatment based on predefined criteria and compare them to untreated controls.[8] The review reports that five published and one current trials performed baseline measurements during run-in and compared trajectories before trial starts and at trial ends. In these studies, the run-in design did not aim to determine participants' eligibility to continue in the trial, rather to establish baseline measurements for comparison after the intervention has been applied. By this approach, the sample size can materially be reduced provided that true between-subject variability in rates is large relative to measurement error[53] and does not influence the internal or external validity if patients are censored according to predefined criteria. In one published study, patients with an ALSFRS-R progression slope improvement ≥15% by clinical trial end were censored as responding to intervention.[54] In a currently ongoing study (NCT03800524), the threshold has been raised to 20%. There has been debate on the meaningful ALSFRS-R slope change. A survey among experienced ALS clinical investigators reported that 25% or higher changes in the ALSFRS-R slope were rated as clinically meaningful, with one third of respondents rating 25% as very clinically meaningful.[55]

Twenty-eight of 76 published studies were sponsored and 16 cosponsored by the pharmaceutical industry. Not all studies sponsored by pharmaceutical companies reported positive results for the primary outcome, while all the studies not sponsored by pharmaceutical companies reported no benefit associated with the primary outcome. Industry sponsorship has previously been associated with increased reporting of positive results.[56] One study sponsored by pharmaceutical company reported benefit in a highly selected population of participants,[19] and three other pharmaceutically sponsored studies with initial negative outcome reported efficacy in a subset of the original subpopulation after post hoc recalculation.[18 57 58] Differently from the prospective design, post hoc analysis must not assume that if an event or intervention precedes another, it is necessarily associated or has causal relationship to the end point chosen.[36] This limitation was encountered in these three studies. Furthermore, narrowing down participants to a selected subset limits generalisability of results.[59] In addition, publication bias could also be associated with decreases in the reporting of negative results, thereby limiting our ability to garner data regarding pharmacological interventions that may not have been associated with any treatment benefits.[60 61]

We report the heterogeneity of medications tested and of study designs. Furthermore, few studies considered potential confounding factors, such as additional clinician-prescribed or self-prescribed treatments (including non-pharmacological interventions), or other potentially disease-modifying activities (eg, exercise). These limitations need to be considered in future clinical trials. Additional directions for future studies include standardisation of measures using data elements recommended by recent consensus.[8] Standardisation will help to control for interstudy differences between participants from baseline to follow-up, providing an opportunity for future meta-analyses to generate definitive conclusions regarding the impact of interventions. One advantage of including heterogeneous studies in our review is that clinicians may appreciate a broad assessment of the current status of the literature and the progressive evolution of clinical trial designs. Notably, most of the studies included in this systematic review did not address the impact of interventions regarding global symptom burden. Few of the reviewed studies included analysis of biomarkers, which may allow assessing individual differences in response to a trial therapy.

The review of clinical trials implementing different constructs highlights proposals for the design of future randomised controlled trials. A priority is to implement eligibility criteria including clinical, genetic and biomarker indicators that take into account prediction models of survival. It is discouraged to perform run-in observations to refine patients' eligibility. Run-in measures may be useful to establish a baseline measure for censoring patients' outcomes. Functional decline and survival stand as the standard, either single or composite, end points for future studies. The use of composite end points does not provide advantages and post hoc analysis is a tangible source of bias when applied to traditional trial designs. Alternative designs may consider event-driven studies, where the trial has no fixed duration and the interim and final analyses are performed once the prespecified number of events is reached.[29] The present review emphasises the importance of designing high-quality clinical trials with adequate generalisability potential. To increase trial quality, there is need to improve current measures of functional decline. An enhanced ALSFRS may provide higher accuracy at different levels of disability and progression, optimise the detection of treatment benefits and cover all relevant domains with a sufficiently wide score range to allow for reliable use as continuous measure. The review also identified patient censoring as a strategy to balance some ALSFRS-R limitations and address differences in individual response without compromising on study quality. Trial design based on patient censoring currently provides a valid strategy for balancing between the probability of type 1 error and the probability of type 2 error in ALS prospective clinical trials.

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**ORCID iDs**
Paolo Tornese http://orcid.org/0000-0002-0252-8007
Alberto Albanese http://orcid.org/0000-0002-5864-0006

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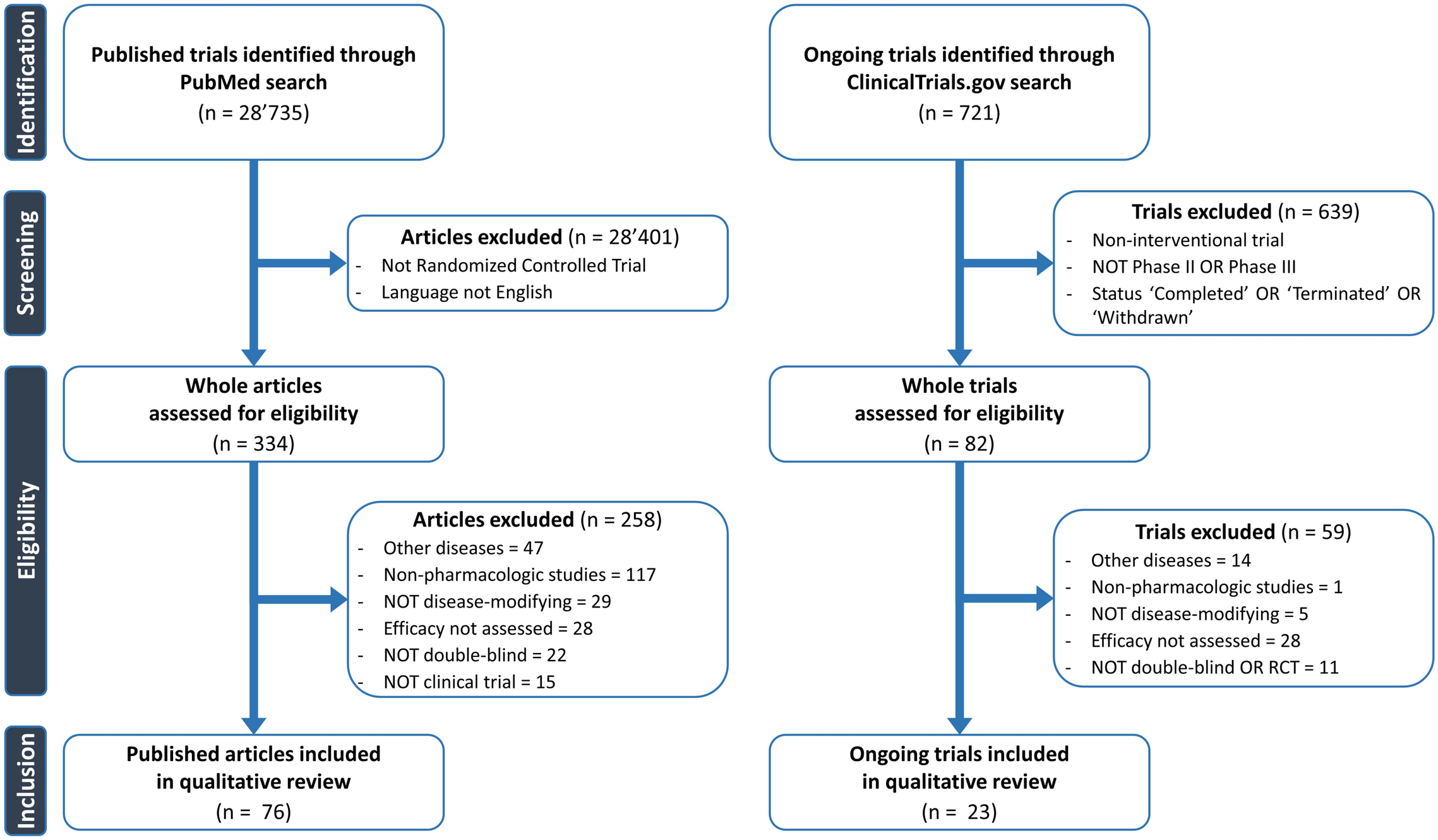
Identification
Screening
Eligibility
Inclusion
Published trials identified through PubMed search
(n = 28’735)
Articles excluded (n = 28’401)
- Not Randomized Controlled Trial
- Language not English
Whole articles assessed for eligibility
(n = 334)
Articles excluded (n = 258)
- Other diseases = 47
- Non-pharmacologic studies = 117
- NOT disease-modifying = 29
- Efficacy not assessed = 28
- NOT double-blind = 22
- NOT clinical trial = 15
Published articles included in qualitative review
(n = 76)
Ongoing trials identified through ClinicalTrials.gov search
(n = 721)
Trials excluded (n = 639)
- Non-interventional trial
- NOT Phase II OR Phase III
- Status ‘Completed’ OR ‘Terminated’ OR ‘Withdrawn’
Whole trials assessed for eligibility
(n = 82)
Trials excluded (n = 59)
- Other diseases = 14
- Non-pharmacologic studies = 1
- NOT disease-modifying = 5
- Efficacy not assessed = 28
- NOT double-blind OR RCT = 11
Ongoing trials included in qualitative review
(n = 23)

**eTable 1.** Characteristics of studies included in systematic review.

| Study drug (Trial #) * | Trial phase | Countries enrolling | Design | Total sample size | Age | Sex ratio (M/F) | Randomization | Run-in observation (months) | Active treatment (months) |
|---|---|---|---|---|---|---|---|---|---|
| Brain gangliosides (Trial 1) | II | USA | Parallel groups | 40 | NA | NA | 1/1 | 0 | 6 |
| Cyclosporine (Trial 2) | II | USA | Parallel groups | 74 | 49.7±3.1 | 2.5/1 | 1/1 | 0 | 12 |
| Branched-chain aminoacids (Trial 3) | II | USA | Parallel groups | 22 | 51.1±11.7 | 6.3/1 | 1/1 | 0 | 12 |
| L-threonine (Trial 4) | II | FRA | Parallel groups | 23 | 59.1±10.5 | 1.3/1 | 1/1 | 0 | 12 |
| Protropin (Trial 5) | II | USA | Parallel groups | 75 | 57.5±10.9 | 1.2/1 | 1/1 | 0 | 18 |
| Lamotrigine (Trial 6) | II | CAN | Parallel groups | 67 | 58.0±11.9 | 1/1 | 1/1 | 0 | 18 |
| Branched-chain aminoacids (Trial 7) | II | ITA | Parallel groups | 126 | 58.5±1.3 | 1.4/1 | 1/1 | 0 | 12 |
| Physostigmine (Trial 8) | II | USA | Crossover | 13 | NA | NA | 1/1 | 3 | 3 or 6 |
| Deprenyl (Trial 9) | II | SWE | Crossover | 10 | 50.0±3.0 | 4/1 | 1/1 | 0 | 3 |
| Riluzole (Trial 10) | II | BEL, FRA | Parallel groups | 155 | 57.5±11.0 | 1.4/1 | 1/1 | 0 | 6 |
| Acetylcysteine (Trial 11) | II | NLD | Parallel groups | 110 | 57.5±10.3 | 1.2/1 | 1/1 | 0 | 12 |
| rhCNTF (Trial 12) | II/III | CAN, USA | Parallel groups | 483 | NA | NA | 1-1-1/1 | 2 to 7 | 6 |
| Nimodipine (Trial 13) | II | CAN, USA | Crossover | 87 | 58.8±11.1 | 1.7/1 | 1/1 | 0 | 3 |
| Dextromethorphan (Trial 14) | II | FRA | Parallel groups | 49 | 64.0±10.0 | 1.5/1 | 1/1 | 0 | 12 |
| rhCNTF (Trial 15) | II/III | USA | Parallel groups | 730 | 54.0 | 1.6/1 | 1-1/1 | 0 | 9 |
| Riluzole (Trial 16) | II/III | BEL, CAN, DEU, ESP, FRA, GBR, USA | Parallel groups | 959 | 56.7±11.0 | 1.5/1 | 1-1-1/1 | 0 | 18 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Branched-chain aminoacids – L-threonine (Trial 17) | II | USA | Parallel groups | 95 | 59.6±10.6 | NA | 1/1 | 0 | 6 |
| Gabapentin (Trial 18) | II | USA | Parallel groups | 149 | 58.5±12.1 | 2.2/1 | 1/1 | 0 | 6 |
| Dextromethorphan (Trial 19) | II | DNK | Parallel groups | 45 | 59.0±9.7 | 1/1 | 1/1 | 0 | 12 |
| rhIGF-I (Trial 20) | II/III | CAN, USA | Parallel groups | 300 | 57.4±1.4 | 1.7/1 | 1-1/1 | 2 to 3 | 9 |
| Selegiline (Trial 21) | II | USA | Parallel groups | 133 | 56.9±1.0 | 1.6/1 | 1/1 | 0 | 6 |
| rhIGF-I (Trial 22) | II | BEL, DEU, FRA, GBR, ITA, NLD, USA | Parallel groups | 183 | NA | NA | 2/1 | 0 | 9 |
| r-metHuBDNF (Trial 23) | III | USA | Parallel groups | 1135 | 55.9±12.5 | 1.9/1 | 1-1/1 | 0 | 9 |
| IFNβ-1a (Trial 24) | II | ITA | Parallel groups | 61 | 57.6±7.0 | 2.2/1 | 1/1 | 3 | 6 |
| Vitamin E (Trial 25) | II | FRA | Parallel groups | 288 | 64.1±10.8 | 1.2/1 | 1/1 | 0 | 12 |
| Gabapentin (Trial 26) | III | USA | Parallel groups | 204 | 61.7 | 1.6/1 | 1/1 | 0 | 9 |
| Riluzole (Trial 27) | III | BEL, FRA | Parallel groups | 168 | 60.4±1.0 | 1/1 | 1/1 | 0 | 18 |
| Creatine monohydrate (Trial 28) | III | NLD | Parallel groups | 175 | 57.7±11.1 | 2.1/1 | 1/1 | 0 | 16 |
| Lamotrigine (Trial 29) | II | SWE | Crossover | 38 | 55.4±13.6 | 1.5/1 | 1/1 | 0 | 4 |
| Topiramate (Trial 30) | III | USA | Parallel groups | 296 | 57.8±12.5 | 1.8/1 | 2/1 | 0 | 12 |
| Xaliproden (Trial 31) | II/III | FRA | Parallel groups | 2077 | 55.8±11.3 | 1.6/1 | 1/1 | 0 | 18 |
| Vitamin E (Trial 32) | II | DEU | Parallel groups | 160 | 58.0±11.0 | 1.9/1 | 1/1 | 0 | 18 |
| Creatine monohydrate (Trial 33) | III | USA | Parallel groups | 104 | 59.0±11.7 | 1.6/1 | 1/1 | 0 | 6 |
| Indinavir (Trial 34) | II | USA | Parallel groups | 46 | 48.7 | 2.5/1 | 1/1 | 0 | 9 |

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|---|---|---|---|---|---|---|---|---|---|
| Pentoxifylline (Trial 35) | II | BEL, DEU, FRA, GBR | Parallel groups | 400 | 56.9±11.9 | 1.8/1 | 1/1 | 0 | 19.5 |
| Celecoxib (Trial 36) | II | USA | Parallel groups | 300 | 54.7±12.0 | 1.9/1 | 2/1 | 0 | 12 |
| TCH346 (Trial 37) | II/III | CAN, CHE, FRA, ITA, USA | Parallel groups | 543 | 55.1±11.4 | 1.8/1 | 1-1-1-1/1 | 4 | 6 |
| Minocycline (Trial 38) | III | USA | Parallel groups | 412 | 58.2±11.4 | 2/1 | 1/1 | 4 | 9 |
| Creatine monohydrate (Trial 39) | II | USA | Parallel groups | 107 | 57.5 | 1.4/1 | 1/1 | 0 | 9 |
| rhIGF-I (Trial 40) | III | USA | Parallel groups | 330 | 54.3 | 1.8/1 | 1/1 | 0 | 24 |
| CoQ10 (Trial 41) | II | USA | Parallel groups | 150 | 57.0±10.9 | 1.3/1 | 1-1/1 | 0 | 9 |
| Valproic acid (Trial 42) | II | NLD | Parallel groups | 163 | 58.0 | 2/1 | 1/1 | 0 | 18 |
| Glatiramer acetate (Trial 43) | II/III | BEL, DEU, FRA, GBR, ISR, ITA | Parallel groups | 366 | 55.2±9.6 | 1.6/1 | 1/1 | 0 | 13 |
| G-CSF (Trial 44) | II | ISR | Parallel groups | 39 | 55.0±11.0 | 1.8/1 | 1/1 | 0 | 6 |
| Lithium carbonate (Trial 45) | II/III | CAN, USA | Parallel groups | 84 | 56.8±11.1 | 1.8/1 | 1/1 | 0 | 13 |
| Talampanel (Trial 46) | II | USA | Parallel groups | 59 | 55.1±10.5 | 2.1/1 | 2/1 | 0 | 9 |
| Memantine (Trial 47) | II/III | PRT | Parallel groups | 63 | 58.6±9.7 | 2/1 | 1/1 | 1 | 12 |
| Growth hormone (Trial 48) | II | ITA | Parallel groups | 40 | 62.7±8.3 | 1.5/1 | 1/1 | 0 | 12 |
| Pioglitazone (Trial 49) | II | DEU | Parallel groups | 219 | 59.0±10.5 | 1.6/1 | 1/1 | 0 | 18 |
| Ursodeoxycholic acid (Trial 50) | III | KOR | Crossover | 63 | 49.1±1.9 | 2.5/1 | 1/1 | 0 | 3 |
| Lithium carbonate (Trial 51) | II | NLD | Parallel groups | 133 | 59.2 | 1.5/1 | 1/1 | 0 | 30 |
| Acetyl-L-carnitine (Trial 52) | II | ITA | Parallel groups | 82 | 62.0 | 1.6/1 | 1/1 | 0 | 12 |
| Lithium carbonate (Trial 53) | III | GBR | Parallel groups | 214 | 59.6±10.7 | 2.2/1 | 1/1 | 0 | 18 |

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|---|---|---|---|---|---|---|---|---|---|
| Dexpramipexole (Trial 54) | III | AUS, CAN, DEU, ESP, IRL, NLD, USA | Parallel groups | 942 | 57.1±11.3 | 1.8/1 | 1/1 | 0 | 18 |
| Olesoxime (Trial 55) | III | BEL, DEU, ESP, FRA, GBR | Parallel groups | 512 | 56.5±11.2 | 1.8/1 | 1/1 | 0 | 18 |
| Ceftriaxone (Trial 56) | III | CAN, USA | Parallel groups | 514 | NA | 1.5/1 | 1/1 | 0 | 18 |
| Edaravone (Trial 57) | III | JPN | Parallel groups | 206 | 58.3 | 1.8/1 | 1/1 | 3 | 9 |
| Erythropoietin (Trial 58) | III | ITA | Parallel groups | 208 | 59.3±9.8 | 1.1/1 | 1/1 | 0 | 18 |
| Tauroursodeoxycholic acid (Trial 59) | II | ITA | Parallel groups | 34 | 56.0±12.5 | 1.9/1 | 1/1 | 3 | 13.5 |
| Flecainide (Trial 60) | II | AUS | Parallel groups | 54 | 53.8±10.2 | 1.5/1 | 1/1 | 3 | 8 |
| Bromocriptine mesylate (Trial 61) | II | JPN | Parallel groups | 36 | 59.2±9.6 | 3/1 | 4/1 | 3 | 3.5 |
| Tiramsetiv (Trial 62) | II | USA | Parallel groups | 605 | 56.5±11.2 | 2.6/1 | 1/1 | 0 | 3 |
| Ozanezumab (Trial 63) | II | AUS, BEL, CAN, DEU, FRA, GBR, ITA, JPN, KOR, NLD, USA | Parallel groups | 303 | 55.6±10.7 | 1.9/1 | 1/1 | 0 | 12 |
| Edaravone (Trial 64) | III | JPN | Parallel groups | 137 | 60.3±10.0 | 1.4/1 | 1/1 | 3 | 6 |
| Edaravone (Trial 65) | II | JPN | Parallel groups | 25 | 57.0 | 1.1/1 | 1/1 | 3 | 9 |
| Curcumin (Trial 66) | II | ITA | Delayed start | 42 | 62.4±11.0 | 0.9/1 | 1/1 | 0 | 3-6 |
| Nanocurcumin (Trial 67) | II | IRN | Parallel groups | 54 | 55.0±11.4 | 2.6/1 | 1/1 | 0 | 12 |
| Rasagiline (Trial 68) | II | DEU | Parallel groups | 251 | 60.2±10.7 | 1.5/1 | 1/1 | 1 | 18 |
| Rasagiline (Trial 69) | II | USA | Parallel groups | 80 | 58.2±9.8 | 2/1 | 3/1 | 0 | 12 |

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|---|---|---|---|---|---|---|---|---|---|
| Tiramsetiv (Trial 70) | III | BEL, CAN, DEU, ESP, FRA, GBR, IRL, ITA, NLD, PRT, USA | Parallel groups | 561 | 57.6±10.3 | 2.2/1 | 2-2-2/3 | 0 | 12 |
| Methylcobalamin (Trial 71) | II/III | JPN | Parallel groups | 370 | 61.8±10.1 | 1.5/1 | 1/1 | 3 | 45.5 |
| EH301 (Trial 72) | II | ESP | Parallel groups | 32 | 56.3±9.8 | 1.7/1 | 1/1 | 0 | 4 |
| Levosimendan (Trial 73) | II | DNK, FIN, GBR, IRL, NLD | Crossover | 66 | 56.5 | 2.5/1 | 1-1/1 | 0 | 0.5 |
| Tamoxifen (Trial 74) | II | TWN | Parallel groups | 18 | 51.6±10.2 | 1.6/1 | 1/1 | 0 | 12 |
| Sodium phenylyrate with tauroursodeoxycholic acid (Trial 75) | II | USA | Parallel groups | 137 | 57.5±9.5 | 2.1/1 | 2/1 | 0 | 6 |
| Masitinib (Trial 76) | II/III | ARG, CAN, ESP, FRA, ITA, MEX | Parallel groups | 394 | 55.2±10.5 | 1.6/1 | 1-1/1 | 0 | 12 |
| Memantine (Trial a) | II | USA | Parallel groups | 90 | NA | NA | NA | 0 | 8 |
| RNS60 (Trial b) | II | NA | Parallel groups | 140 | NA | NA | NA | 0 | 6 |
| Perampanel (Trial c) | II | JPN | Parallel groups | 60 | NA | NA | NA | 3 | 12 |
| Interleukin-2 (Trial d) | II | FRA, GBR | Parallel groups | 304 | NA | NA | 1/1 | 0 | 18 |
| Masitinib (Trial e) | III | DEU, USA | Parallel groups | 495 | NA | NA | NA | 3 | 12 |
| Pimozide (Trial f) | II | CAN | Parallel groups | 100 | NA | NA | NA | 0 | 5.5 |
| NurOwn (Trial g) | III | USA | Parallel groups | 261 | NA | NA | 1/1 | 3 | 4 |
| Deferiprone (Trial h) | II/III | FRA | Parallel groups | NA | NA | NA | 1/1 | 0 | 12 |

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|---|---|---|---|---|---|---|---|---|---|
| Arimoclomol (Trial i) | III | BEL, CAN, CHE, DEU, ESP, FRA, GBR, ITA, NLD, POL, SWE, USA | Parallel groups | 231 | NA | NA | NA | 0 | 19 |
| MediCabilis CBD Oil (Trial j) | III | AUS | Parallel groups | 30 | NA | NA | 1/1 | 0 | 6 |
| Colchicine (Trial k) | II | ITA | Parallel groups | 54 | NA | NA | 1-1/1 | 0 | 7.5 |
| Tauroursodeoxycholic Acid (Trial l) | III | BEL, DEU, FRA, GBR, IRL, ITA, NLD | Parallel groups | 440 | NA | NA | NA | 3 | 18 |
| Ibudilast (Trial m) | II/III | CAN, USA | Parallel groups | 230 | NA | NA | 1/1 | 0 | 12 |
| Cu(II)ATSM (Trial n) | II/III | AUS | Parallel groups | 80 | NA | NA | 1/1 | 0 | 6 |
| CNM-Au8 (Trial o) | II | AUS | Parallel groups | 42 | NA | NA | 1/1 | 0 | 9 |
| Vitamin E (Trial p) | II | MYS | Parallel groups | 20 | NA | NA | NA | 3 | 6 |
| Ravulizumab (Trial q) | III | AUS, BEL, CAN, CHE, DEU, DNK, ESP, FRA, GBR, IRL, ISR, ITA, JPN, NLD, POL, SWE, USA | Parallel groups | 354 | NA | NA | NA | 0 | 12.5 |
| Memantine – Trazodone (Trial r) | II/III | GBR | Parallel groups | 750 | NA | NA | 1/1 | 0 | 18 |
| CNM-Au8 (Trial s) | II/III | USA | Parallel groups | 160 | NA | NA | 3/1 | 0 | 6 |
| Verdiperstat (Trial t) | II/III | USA | Parallel groups | 160 | NA | NA | 3/1 | 0 | 6 |
| Zilucoplan (Trial u) | II/III | USA | Parallel groups | 160 | NA | NA | 3/1 | 0 | 6 |
| Pridopidine (Trial v) | II/III | USA | Parallel groups | 160 | NA | NA | 3/1 | 0 | 6 |

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|---|---|---|---|---|---|---|---|---|---|
| Pegcetacoplan (Trial w) | II | AUS, BEL, CZE, DEU, ESP, FRA, ITA, POL, USA | Parallel groups | 228 | NA | NA | NA | 0 | 13 |

* Trials are referenced in eTable 3. NA: Not available.

**Abbreviations for study drugs:** CBD, cannabidiol; CoQ10, coenzyme Q10; G-CSF, granulocyte-colony stimulating factor; IFNß-1a, interferon beta-1a; r-metHuBDNF, recombinant human methionyl brain-derived neurotrophic factor; rhCNTF, recombinant human ciliary neurotrophic factor; rhIGF-I, recombinant human insulin-like growth factor type I.

**Abbreviations for countries:**: ARG, Argentina; AUS, Australia; BEL, Belgium; CAN, Canada; CHE, Switzerland; CZE, Czech Republic; DEU, Germany; DNK, Denmark; ESP, Spain; FIN, Finland; FRA, France; GBR, United Kingdom; IRL, Ireland; IRN, Iran; ISR, Israel; ITA, Italy; JPN, Japan; KOR, South Korea; MEX, Mexico; MYS, Malaysia; NLD, Netherlands; POL, Poland; PRT, Portugal; SWE, Sweden; TWN, Taiwan; USA, United States of America.

**Randomization** is indicated as ratio number of patients on active or placebo treatments; different doses of active treatment are shown by a dash (-).

**eTable2.** Main eligibility criteria of studies included in systematic review.

| **Study drug (Trial #) *** | **Inclusion** | | | | | **Exclusion** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Diagnostic criteria** | **Disease duration (months)** | **Concomitant ALS treatment** | **Vital capacity criteria** | **Age** | **ALS subtypes criteria** | **Familial or genetic criteria** | **Respiratory function criteria** | **Swallowing function criteria** |
| Brain gangliosides (Trial 1) | Clinical judgment | NA | NA | NA | NA | NA | NA | NA | NA |
| Cyclosporine (Trial 2) | Clinical judgment | <36 | NA | NA | 25 to 65 | LMN, PBP | NA | NA | NA |
| Branched-chain aminoacids (Trial 3) | Clinical judgment | NA | NA | NA | NA | NA | NA | NA | NA |
| L-threonine (Trial 4) | Clinical judgment | <36 | NA | NA | NA | NA | NA | NA | NA |
| Protropin (Trial 5) | Clinical judgment | NA | NA | NA | NA | PBP, PLS, PMA | NA | NA | NA |
| Lamotrigine (Trial 6) | Clinical judgment | <12 | NA | NA | NA | MMA, PLS, PMA | Familial occurrence | NA | NA |
| Branched-chain aminoacids (Trial 7) | Clinical judgment | <24 | NA | FVC >50% | 30 to 80 | NA | Familial occurrence | MV | Norris scale items 3 and 6 <2 or PEG feeding |
| Physostigmine (Trial 8) | EE | NA | NA | FVC >50% | NA | NA | Familial occurrence | NA | NA |
| Deprenyl (Trial 9) | EE | NA | NA | NA | NA | NA | NA | NA | NA |
| Riluzole (Trial 10) | Pr, D – EE | <60 | NA | FVC >60% | 20 to 75 | NA | Not excluded | T | NA |
| Acetylcysteine (Trial 11) | Pr, D – EE | NA | NA | NA | 20 to 80 | NA | Familial occurrence | NA | NA |
| rhCNTF (Trial 12) | Clinical judgment | <36 | NA | FVC >70% | 21 to 85 | PBP | Familial occurrence | NA | NA |

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|---|---|---|---|---|---|---|---|---|---|
| Nimodipine (Trial 13) | EE | NA | Riluzole - | NA | 25 to 75 | NA | Familial occurrence | NA | NA |
| Dextromethorphan (Trial 14) | Pr, D – EE | NA | NA | NA | NA | NA | NA | NA | NA |
| rhCNTF (Trial 15) | NA | NA | Riluzole - | NA | NA | NA | NA | NA | NA |
| Riluzole (Trial 16) | Pr, D – EE | <60 | NA | FVC/SVC >70% | 18 to 75 | NA | Not excluded | T | NA |
| Branched-chain aminoacids – L-threonine (Trial 17) | Clinical judgment | <24 | Riluzole - | NA | 30 to 85 | PBP | NA | NA | NA |
| Gabapentin (Trial 18) | Pr, D – EE | <36 | Riluzole - | FVC >60% | 21 to 85 | PBP | NA | NA | NA |
| Dextromethorphan (Trial 19) | NA | <24 | Riluzole - | FVC >50% | 25 to 80 | LMN, PBP, PLS | Familial occurrence | NA | NA |
| rhIGF-I (Trial 20) | Pr, D – EE | <36 | Riluzole - | FVC >50% | >20 | PBP, PLS, PMA | Familial occurrence | NA | NA |
| Selegiline (Trial 21) | Clinical judgment | <36 | Riluzole - | NA | 25 to 65 | LMN, PLS | NA | NA | NA |
| rhIGF-I (Trial 22) | Pr, D – EE | <36 | Riluzole - | FVC >50% | >20 | PBP, PLS, PMA | Familial occurrence | NA | NA |
| r-metHuBDNF (Trial 23) | Pr, D – EE | NA | Riluzole ± | NA | 21 to 80 | NA | Not excluded | NA | NA |
| IFNβ-1a (Trial 24) | Clinical judgment | 6 to 24 | Riluzole - | NA | 40 to 70 | PBP, PLS, PMA | Familial occurrence | NA | NA |
| Vitamin E (Trial 25) | Pr, D – EE | <60 | Riluzole + | FVC >60% | >18 | NA | NA | NA | NA |
| Gabapentin (Trial 26) | Pr, D – EE | <36 | Riluzole - | FVC >60% | 21 to 85 | PBP | NA | NA | NA |
| Riluzole (Trial 27) | Pr, D – EE | <60 | NA | NA | NA | NA | Not excluded | T | NA |
| Creatine monohydrate (Trial 28) | Pr, D – EE | 6 to 60 | Riluzole + | FVC >60% | 18 to 75 | NA | Not excluded | MV, T | NA |

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|---|---|---|---|---|---|---|---|---|---|
| Lamotrigine (Trial 29) | Pr, D – EE | NA | Riluzole - | NA | NA | NA | NA | NA | NA |
| Topiramate (Trial 30) | Pr, D – EE | <36 | Riluzole ± | FVC >50% | 18 to 80 | NA | Not excluded | NA | NA |
| Xaliproden (Trial 31) | Pr, D – EE | 6 to 60 | Riluzole ± | FVC >60% | 18 to 75 | NA | Not excluded | MV, T | Norris scale item 3 =0 or PEG feeding |
| Vitamin E (Trial 32) | Pr, D – EE | <60 | Riluzole + | NA | NA | NA | Not excluded | NA | NA |
| Creatine monohydrate (Trial 33) | Pr, D – EE | <60 | Riluzole ± | FVC >50% | 18 to 80 | NA | Not excluded | NA | NA |
| Indinavir (Trial 34) | Pr, D – EE | NA | Riluzole ± | FVC >50% | 18 to 85 | NA | NA | MV | NA |
| Pentoxifylline (Trial 35) | Pr, D – EE | 6 to 48 | Riluzole + | NA | 18 to 80 | NA | NA | NA | NA |
| Celecoxib (Trial 36) | Clinical judgment | <60 | Riluzole ± | FVC >60% | >18 | NA | Not excluded | NA | NA |
| TCH346 (Trial 37) | Pr, D – EER | <36 | Riluzole ± | FVC >70% | 21 to 80 | NA | NA | NA | NA |
| Minocycline (Trial 38) | Pr, D – EER | <36 | Riluzole ± | FVC >75% | 21 to 85 | NA | Familial occurrence | NIV, T | NA |
| Creatine monohydrate (Trial 39) | Pr, D – EER | <60 | Riluzole ± | NA | 21 to 80 | NA | Not excluded | NIV, T | NA |
| rhIGF-I (Trial 40) | Pr, D – EE | <30 | Riluzole ± | FVC >60% | >18 | NA | Not excluded | T | NA |
| CoQ10 (Trial 41) | Pr, D – EER | <60 | Riluzole ± | FVC >60% | 21 to 85 | NA | Not excluded | NA | NA |
| Valproic acid (Trial 42) | Pr, D – EER | 6 to 36 | Riluzole + | FVC >70% | 18 to 75 | NA | NA | NIV, T | NA |
| Glatiramer acetate (Trial 43) | Pr, D – EE | <36 | Riluzole + | SVC >70% | 18 to 70 | NA | Not excluded | NIV, MV | PEG feeding |
| G-CSF (Trial 44) | Pr, D – EER | <72 | Riluzole ± | FVC >50% | 18 to 85 | NA | Familial occurrence | NA | NA |
| Lithium carbonate (Trial 45) | Po, Pr, D – EER | <36 | Riluzole + | SVC >60% | >18 | NA | Not excluded | NA | NA |
| Talampanel (Trial 46) | Pr, D – EE | <24 | Riluzole ± | FVC >60% | 18 to 85 | NA | Not excluded | NA | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Memantine (Trial 47) | Pr, D – EER | <36 | Riluzole + | FVC >60% | 18 to 75 | NA | NA | T | PEG feeding |
| Growth hormone (Trial 48) | Pr, D – EE | <36 | Riluzole + | NA | 40 to 85 | NA | Not excluded | T | PEG feeding |
| Pioglitazone (Trial 49) | Po, Pr, D – EER | <36 | Riluzole + | SVC 50% to 95% | NA | Other MNDs | NA | NIV, T | PEG feeding |
| Ursodeoxycholic acid (Trial 50) | Pr, D – EER | <60 | Riluzole + | FVC >30% | >20 | NA | Familial occurrence | NA | NA |
| Lithium carbonate (Trial 51) | Pr, D – EER | 6 to 36 | Riluzole + | FVC >70% | 18 to 85 | Other MNDs | Not excluded | NIV, T | NA |
| Acetyl-L-carnitine (Trial 52) | Pr, D – EER | 6 to 36 | Riluzole + | FVC >80% | 40 to 70 | Other MNDs | Familial occurrence | NIV, T | PEG feeding |
| Lithium carbonate (Trial 53) | Po, Pr, D – EER | 6 to 36 | Riluzole + | SVC >65% | >18 | NA | Not excluded | NA | NA |
| Dexpramipexole (Trial 54) | Po, Pr, D – EER | <24 | Riluzole ± | SVC >70% | 18 to 80 | NA | Not excluded | NA | NA |
| Olesoxime (Trial 55) | Pr, D – EER | 6 to 36 | Riluzole + | SVC >70% | 18 to 80 | NA | NA | NA | NA |
| Ceftriaxone (Trial 56) | Po, Pr, D – EER | <36 | Riluzole ± | FVC >60% | >18 | NA | Not excluded | MV | NA |
| Edaravone (Trial 57) | Po, Pr, D – EER | <36 | Edaravone + | FVC >70% | 20 to 75 | NA | Not excluded | NA | NA |
| Erythropoietin (Trial 58) | Pr, D – EER | <18 | Riluzole + | SVC >75% | 18 to 75 | PBP | Familial occurrence | NIV, T | NA |
| Tauroursodeoxycholic acid (Trial 59) | Pr, D – EER | <18 | Riluzole + | FVC >75% | 18 to 75 | PBP | NA | T | NA |
| Flecainide (Trial 60) | Pr, D – EER | <60 | Riluzole + | NA | 18 to 75 | NA | Not excluded | NA | NA |
| Bromocriptine mesylate (Trial 61) | Po, Pr, D – EER | <36 | Riluzole + | FVC >70% | 20 to 75 | NA | Not excluded | NA | NA |
| Tiramsetiv (Trial 62) | Po, Pr, D – EER | NA | Riluzole ± | SVC >45% | NA | NA | Not excluded | NA | NA |
| Ozanezumab (Trial 63) | Po, Pr, D – EER | <30 | Riluzole ± | SVC >65% | 18 to 80 | MMA, PLS | Not excluded | NIV, MV | NA |

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|---|---|---|---|---|---|---|---|---|---|
| Edaravone (Trial 64) | Pr, D – EER | <24 | Edaravone + | FVC >80% | 20 to 75 | NA | Not excluded | ALSFRS-R item 10 <3 | NA |
| Edaravone (Trial 65) | Pr, D – EER | <36 | Edaravone + | FVC >60% | 20 to 75 | NA | Not excluded | ALSFRS-R item 10 <3 | NA |
| Curcumin (Trial 66) | Po, Pr, D – EER | NA | Riluzole ± | NA | 18 to 85 | NA | Not excluded | T | NA |
| Nanocurcumin (Trial 67) | Pr, D – EER | NA | Riluzole + | NA | 18 to 85 | NA | Familial occurrence | MV | NA |
| Rasagiline (Trial 68) | Po, Pr, D – EER | <36 | Riluzole + | SVC >50% | >18 | Other MNDs | NA | MV, T | PEG feeding |
| Rasagiline (Trial 69) | Pr, D – EER | <24 | Riluzole ± | FVC >75% | 21 to 80 | NA | NA | NIV, T | NA |
| Tiramsetiv (Trial 70) | Pr, D – EER | NA | Riluzole ±, Edaravone - | SVC >70% | NA | NA | NA | NA | NA |
| Methylcobalamin (Trial 71) | Pr, D – EER | <36 | Riluzole ± | FVC >60% | >20 | NA | Not excluded | NIV, T | NA |
| EH301 (Trial 72) | Pr, D – EER | >6 | Riluzole + | NA | >18 | NA | Not excluded | NIV, T | PEG feeding |
| Levosimendan (Trial 73) | Pr, D – EER | 12 to 48 | Riluzole + | SVC 60% to 90% | NA | NA | Not excluded | NIV | PEG feeding |
| Tamoxifen (Trial 74) | Pr, D – EER | NA | Riluzole + | NA | 20 to 65 | NA | Specific mutations (FUS, SOD-1) | MV | NA |
| Sodium phenylyrate with tauroursodeoxycholic acid (Trial 75) | D – EER | <18 | Riluzole ±, Edaravone ± | SVC >60 | 18 to 80 | NA | NA | NA | NA |
| Masitinib (Trial 76) | Pr, D – EER | <36 | Riluzole + | FVC >60% | 18 to 75 | NA | NA | NA | PEG feeding |
| Memantine (Trial a) | Po, Pr, D – EER | NA | Riluzole ±, Edaravone ± | FVC >60% | 18 to 85 | NA | NA | NA | NA |
| RNS60 (Trial b) | Pr, D – EER | <36 | Riluzole + | NA | 18 to 80 | Other MND | Not excluded | NA | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Perampanel (Trial c) | Pr, D – EER | <24 | Riluzole ±, Edaravone - | FVC >80% | 40 to 78 | PBP | NA | NIV, T | NA |
| Interleukin-2 (Trial d) | Po, Pr, D – EER | <24 | Riluzole + | SVC >70% | 18 to 75 | NA | NA | NA | PEG feeding |
| Masitinib (Trial e) | Pr, D – EER | <24 | Riluzole + | FVC >60% | 18 to 81 | NA | Not excluded | NA | NA |
| Pimozide (Trial f) | Pr, D – EER | <48 | Riluzole ±, Edaravone ± | SVC >50% | >18 | NA | NA | NA | NA |
| NurOwn (Trial g) | Po, Pr, D – EER | <24 | Riluzole ±, Edaravone - | SVC >65% | 18 to 60 | NA | NA | NIV, MV, T | PEG feeding |
| Deferiprone (Trial h) | Po, Pr, D – EER | <18 | Riluzole ± | SVC >75% | 18 to 75 | NA | NA | NA | NA |
| Arimoclomol (Trial i) | Po, Pr, D – EER | <18 | NA | SVC >70% | >18 | NA | Not excluded | NIV, MV, T | NA |
| MediCabilis CBD Oil (Trial j) | Pr, D – EER | <24 | NA | FVC >60% | 25 to 80 | NA | NA | NA | NA |
| Colchicine (Trial k) | Pr, D – EER | <18 | Riluzole + | FVC >65% | 18 to 80 | FAS, FLS, PLS, PMA, UMN | Familial occurrence, specific mutations (C9ORF72, FUS, SOD-1, TDP-43) | NIV, T | PEG feeding |
| Tauroursodeoxycholic Acid (Trial l) | Pr, D – EER | <18 | Riluzole +, Edaravone - | FVC >70% | 18 to 80 | NA | Not excluded | NIV, MV, T | ALSFRS-R item 3 <4 |
| Ibudilast (Trial m) | Pr, D – EER | <18 | Riluzole ±, Edaravone ± | NA | 18 to 80 | NA | Not excluded | T | NA |
| Cu(II)ATSM (Trial n) | AS | NA | Riluzole ± | NA | 18 to 75 | NA | Not excluded | NA | NA |
| CNM-Au8 (Trial o) | Po, Pr, D – AS | <24 | Riluzole ± | FVC >60% | 30 to 80 | NA | Familial occurrence | NIV, T | PEG feeding |
| Vitamin E (Trial p) | NA | <24 | NA | NA | NA | NA | NA | NIV | PEG feeding |
| Ravulizumab (Trial q) | Po, Pr, D – EER | <36 | Riluzole ± | SVC >65% | >18 | NA | Not excluded | NIV, MV | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Memantine – Trazodone (Trial r) | Po, Pr, D – EER | NA | NA | NA | >18 | NA | NA | NA | NA |
| CNM-Au8 (Trial s) | Po, Pr, D – EER | <36 | Riluzole ±, Edaravone ± | FVC/SVC >50% | >18 | NA | Not excluded | NA | NA |
| Verdiperstat (Trial t) | Po, Pr, D – EER | <36 | Riluzole ±, Edaravone ± | FVC/SVC >50% | >18 | NA | Not excluded | NA | NA |
| Zilucoplan (Trial u) | Po, Pr, D – EER | <36 | Riluzole ±, Edaravone ± | FVC/SVC >50% | >18 | NA | Not excluded | NA | NA |
| Pridopidine (Trial v) | Po, Pr, D – EER | <36 | Riluzole ±, Edaravone ± | FVC/SVC >50% | >18 | NA | Not excluded | NA | NA |
| Pegcetacoplan (Trial w) | Pr, D – EER | <18 | Riluzole ±, Edaravone ± | SVC >60% | >18 | NA | Familial occurrence | NA | NA |

* Trials are referenced in eTable 3. NA: Not available.

**Abbreviations for study drugs:** CBD, cannabidiol; CoQ10, coenzyme Q10; G-CSF, granulocyte-colony stimulating factor; IFNß-1a, interferon beta-1a; r-metHuBDNF, recombinant human methionyl brain-derived neurotrophic factor; rhCNTF, recombinant human ciliary neurotrophic factor; rhIGF-I, recombinant human insulin-like growth factor type I.

**Abbreviations for diagnostic criteria:** AS, Awaji-Shima criteria; EE, El-Escorial criteria; EER, El-Escorial Revised criteria; D, Definite; Po, Possible; Pr, Probable; NA, data not available.

**Concomitant ALS treatment at inclusion** shows a plus (+) sign for acceptable concomitant medications, a minus (-) sign for unacceptable concomitant medications, and a plus-minus (±) sign for indifferent concomitant medications.

**Abbreviations for vital capacity criteria at inclusion:** FVC, forced vital capacity; SVC, slow vital capacity; NA, data not available.

**Abbreviations for ALS subtype exclusion criteria:** FAS, flail arm syndrome; FLS, flail leg syndrome; LMN, lower motor neuron; MMA, Monomelic amyotrophy; MND, motor neuron disease; PBP, progressive bulbar palsy; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; UMN, upper motor neuron; NA, data not available.

**Abbreviations for familial or genetic exclusion criteria:** C9ORF72, chromosome 9 open reading frame 72; FUS, fused in sarcoma; SOD-1, superoxide dismutase 1; TDP-43, TAR DNA-binding protein 43; NA, data not available.

**Abbreviations for respiratory function exclusion criteria:** ALSFRS-R, Amyotrophic lateral sclerosis functional rating scale-revised; MV, mechanical ventilation; NIV, non-invasive ventilation; T, tracheostomy; NA, data not available.

**Abbreviations for swallowing function exclusion criteria:** ALSFRS-R, Amyotrophic lateral sclerosis functional rating scale-revised; PEG, percutaneous endoscopic gastrostomy; NA, data not available.

**eTable 3.** List of 76 published and 24 current trials included in the review. The trials are listed in chronological order and referenced by numbers (published trials), or by letters (ongoing trials).

**Published trials**


1. Bradley WG, Hedlund W, Cooper C, et al. A double-blind controlled trial of bovine brain gangliosides in amyotrophic lateral sclerosis. *Neurology* 1984; **34**(8): 1079-82.
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**Ongoing trials**

a. Multi-centered Double Blind, Placebo Controlled Study Evaluating the Safety and Efficacy of Memantine at 20 mg BID in Patients With ALS. https://ClinicalTrials.gov/show/NCT02118727
b. Nebulized RNS60 for the Treatment of Amyotrophic Lateral Sclerosis. https://ClinicalTrials.gov/show/NCT02988297
c. Perampanel for Sporadic Amyotrophic Lateral Sclerosis (ALS): A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 2 Trials. https://ClinicalTrials.gov/show/NCT03019419
d. Efficacy and Safety of Low-dose IL-2 (Ld-IL-2) as a Treg Enhancer for Controlling Neuro-inflammation in Newly Diagnosed Amyotrophic Lateral Sclerosis (ALS) Patients: A Randomized, Double-blind, Placebo-Controlled, Phase-II Proof of Concept/ Proof of Mechanism Clinical Trial. https://ClinicalTrials.gov/show/NCT03039673
e. A Prospective, Multicenter, Randomised, Double-blind, Placebo-controlled, Parallel Groups, Phase 3 Study to Compare the Efficacy and Safety of Masitinib in Combination With Riluzole Versus Placebo in Combination With Riluzole in the Treatment of Patients Suffering From Amyotrophic Lateral Sclerosis (ALS). https://ClinicalTrials.gov/show/NCT03127267
f. A Phase II Randomized, Placebo-Controlled, Double Blinded, Multi-Centre Clinical Trial of Pimozide in Patients With Amyotrophic Lateral Sclerosis. https://ClinicalTrials.gov/show/NCT03272503
g. Safety and Efficacy of Repeated Administrations of NurOwn® in ALS Patients. https://ClinicalTrials.gov/show/NCT03280056
h. Conservative Iron Chelation as a Disease-modifying Strategy in Amyotrophic Lateral Sclerosis: Multicentre, Parallel-group, Placebo-controlled, Randomized Clinical Trial of Deferiprone. https://ClinicalTrials.gov/show/NCT03293069
i. A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotropic Lateral Sclerosis. https://ClinicalTrials.gov/show/NCT03491462

j. A Randomised, Double-blind, Single-centre Study on the Safety, Tolerability and Efficacy of Cannabis Based Medicine Extract (MediCabilis CBD Oil) in Slowing the Disease Progression in Amyotrophic Lateral Sclerosis or Motor Neurone Disease Patients. https://ClinicalTrials.gov/show/NCT03690791
k. Colchicine for Amyotrophic Lateral Sclerosis: a Phase II, Randomized, Double Blind, Placebo Controlled, Multicenter Clinical Trial. https://ClinicalTrials.gov/show/NCT03693781
l. Safety and Efficacy of Tauroursodeoxycholic (TUDCA) as add-on Treatment in Patients Affected by Amyotrophic Lateral Sclerosis (ALS). https://ClinicalTrials.gov/show/NCT03800524
m. A Phase 2b/3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 12 Month Clinical Trial to Evaluate the Efficacy and Safety of MN-166 (Ibudilast) Followed by Open-Label Extension Phase in Subjects With Amyotrophic Lateral Sclerosis. https://ClinicalTrials.gov/show/NCT04057898
n. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of Cu(II)ATSM in Patients With Amyotrophic Lateral Sclerosis/Motor Neuron Disease. https://ClinicalTrials.gov/show/NCT04082832
o. Therapeutic Nanocatalysis to Slow Disease Progression of Amyotrophic Lateral Sclerosis (ALS) (RESCUE-ALS). https://ClinicalTrials.gov/show/NCT04098406
p. The Efficacy and Safety of Vitamin E Mixed Tocotrienols In Patients With Amyotrophic Lateral Sclerosis (ALS) : A Pilot Exploratory Study. https://ClinicalTrials.gov/show/NCT04140136
q. A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS). https://ClinicalTrials.gov/show/NCT04248465
r. Motor Neurone Disease - Systematic Multi-Arm Adaptive Randomised Trial. https://ClinicalTrials.gov/show/NCT04302870
s. HEALEY ALS Platform Trial - Regimen C CNM-Au8. https://ClinicalTrials.gov/show/NCT04414345
t. HEALEY ALS Platform Trial - Regimen B Verdiperstat. https://ClinicalTrials.gov/show/NCT04436510
u. HEALEY ALS Platform Trial - Regimen A Zilucoplan. https://ClinicalTrials.gov/show/NCT04436497
v. HEALEY ALS Platform Trial - Regimen D Pridopidine. https://ClinicalTrials.gov/show/NCT04615923
w. A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Subjects With Amyotrophic Lateral Sclerosis (ALS). https://ClinicalTrials.gov/show/NCT04579666
x. Phase III Trial of AMX0035 for Amyotrophic Lateral Sclerosis Treatment (Phoenix). https://ClinicalTrials.gov/show/NCT05021536