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Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS)

Draft

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This guideline replaces Points to consider on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (CPMP/EWP/565/98).

Comments should be provided using this template. The completed comments form should be sent to CNSWPSecretariat@ema.europa.eu

Keywords	***Amyotrophic lateral sclerosis (ALS), Motor neuron disease, Guidance***

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Executive summary

Amyotrophic lateral sclerosis (ALS) is a rare progressive, fatal motor neuron disease characterised by axonal degeneration and progressive loss of the upper and lower motor neurons throughout the central nervous system. Considering the seriousness of the disease and limited options for treatment there remains an unmet medical need for efficacious and safe treatments for ALS. The main requirements for medicinal products for the treatment of ALS with respect to diagnostic criteria, study endpoints and trial design are reviewed and redefined.

This document replaces and updates the previous Points to consider on ALS and focuses on the design of studies for disease-modifying as well as symptomatic treatments in this therapeutic area, the choice of meaningful outcome parameters and the clinical relevance of functional tests of disability including motor and respiratory functions and their relationship to survival.

The present document should be considered as general guidance on the development of medicinal products for the treatment of Amyotrophic lateral sclerosis (ALS) and should be read in conjunction with other relevant EMA and ICH guidelines.

1. Introduction (background)

The reported incidence of ALS varies from 0.3-2.5 per 100 000 persons per year. The exact pathophysiology of ALS is still uncertain with emerging evidence of a complex interaction between genetic and molecular pathways (Kiernan 2011, Pratt 2012). Motor neuron damage has been attributed to oxidative damage, changes in intracellular calcium levels, glutamate excitoxicity and genetic factors (Guerney 1994; Leigh 2004). A growing number of ALS-causing genes have been identified recently and are now under investigation to provide more insight in the etiology of the disease (Deng 2012; Al-Chalabi 2012). There is genetic overlap between ALS and other progressive neurodegenerative syndromes such as frontotemporal dementia (FTD) (DeJesus-Hernandez 2011; Orr 2011; Pratt 2012; Ludolph 2012).

Sporadic ALS (SALS) accounts for the vast majority of cases whereas only a small fraction of cases are familial, with a Mendelian pattern of inheritance (FALS) (Kiernan 2011). Although FALS is clinically and genetically heterogeneous (Chen 2004) the clinical presentation of FALS and SALS can be very similar. The mean age of onset for ALS varies between 58–63 years for sporadic disease and 47-52 years for familial disease (Kiernan 2011; Logroscino 2010). Presentation before 25 years of age is rare and usually termed as juvenile ALS (JALS) (Aggarwal 2006, Zou 2013). While several forms of genetically defined juvenile ALS have been characterized (Chance 1998, Rabin 1999, Orban 2007, Belzil 2012) only very few sporadic cases of juvenile-onset ALS have been reported and are thought to be a distinct clinical entity (Gouveia 2007, Bäumer 2010).

In sporadic ALS men are more commonly affected than women (1.4-2.5:1) although the number of women affected increases with older age groups. Median survival time is about 2-3 years, however, about 20% of patients may be alive after 5 years and a small percentage even after 10 years (Talbot 2009).

The main presentations of ALS include limb-onset ALS with a combination of upper and lower motor neuron (UMN and LMN) signs in the limbs (70%) and bulbar onset ALS, presenting with speech and swallowing difficulties, and with limb features developing later in the course of the disease (25%). In addition there are less common presentations such as truncal-abdominal (axial) involvement or

respiratory involvement at onset and onset with weight loss, fasciculation and cramps. Primary lateral sclerosis with pure UMN involvement and progressive muscular atrophy with pure LMN involvement have slower progression and better prognosis and are not considered to be typical ALS (Gordon 2006).

Patients with ALS experience progressive denervation and atrophy of skeletal muscles and in the majority of cases die from respiratory failure. Prognostically unfavourable factors are older age at time of onset of symptoms, short time from first symptoms to diagnosis, bulbar onset and worsening respiratory function. Associations with other neurodegenerative diseases such as FTD are also reported to be associated with higher progression rates.

Treatment of ALS is mainly palliative and consists primarily of supportive measures (EFNS guideline 2012).

2. Scope

This Guideline is intended to provide guidance for the evaluation of drugs for the treatment of ALS. Primary lateral sclerosis with pure UMN involvement and progressive muscular atrophy with pure LMN involvement are presently not within the scope of this guideline. The guideline focuses on treatment aimed to modify disease progression. In addition, some guidance is given on symptomatic treatment of muscle strength. At the time of the development of the guideline the most up-to-date research data and data from available clinical trials in ALS have been taken into account . However, the guideline may need amending according to future scientific and clinical findings.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83 as amended and in conjunction with the following guidelines:

- Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (ICH E6);
- Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8);
- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4);
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9);
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10);
- Point to consider on adjustment for baseline covariates – CHMP/EWP/2863/99;
- Guideline on missing data in confirmatory clinical trials – CPMP/EWP/1776/99;
- Points to consider on Multiplicity issues in clinical trials - CPMP/EWP/908/99;
- Regulation No (EC) 141/2000 on orphan medicinal products;
- Guideline on Clinical Trials in small populations CHMP/EWP/83561/05;

- Points to consider on application with 1. Meta-analysis; 2. one pivotal study - CPMP/EWP/2330/99;

- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1);

- Studies in support of special populations: geriatrics - CPMP/ICH/379/99 (ICH E7);

- Pharmacokinetic studies in man - EudraLex vol. 3C C3A;

- Note for guidance on the investigation of drug interactions CPMP/EWP/560/95

4. General strategy for developing products for the treatment of ALS

4.1. General strategy

The strategy for demonstrating efficacy will depend on the mechanism of action of the new product and whether it is expected to have disease modifying activity or whether the treatment effect is expected to be purely symptomatic. Studies should be randomized, double-blind and placebo-controlled (see section 8). For disease modifying treatments the clinical development strategy also needs to consider whether the new product is intended to be used in combination with current standard treatment (i.e. riluzole), whether it is to be developed as an alternative monotherapy, or whether both monotherapy and combination therapy are envisaged.

4.2. Study Objectives

The primary goal of ALS treatment is the prevention or delay of disease progression, although symptomatic treatment is also important.

The following study objectives could be considered:

- Increased survival
- Delay or stabilisation of disease progression
- Improvement of symptoms of ALS

While future studies may seek to demonstrate efficacy for primary prevention of the disease, particularly in familial ALS, proper guidance cannot yet be provided concerning trials with this objective as there are no data in support of recommendations.

Improvement in quality of life or reduction of the rate of deterioration of quality of life may be an important secondary study objective.

5. Patients characteristics and selection of patients

5.1. Diagnostic criteria

Due to the variability in clinical findings early in the course of the disease and the lack of an established biomarker definite early diagnosis can be difficult. Symptoms are often not recognized until considerable motor function has been lost and the mean delay in time from presentation to diagnosis is still approximately 1 year (Mitchell 2010; Bowser 2011). Diagnosis of ALS may be straightforward if the patient presents with progressive, generalized symptoms in the bulbar and limb regions. However, selection of a homogeneous study population early in the course of the disease might be difficult due to the delay in diagnosis and differences in prognosis depending on the clinical presentation of the disease. Study participants should be stratified according to known prognostic factors, i.e. bulbar signs and time from first symptom to diagnosis (Beghi 2011).

Several candidate protein-based, neurophysiological and neuroimaging biomarkers for ALS have been identified but until now none of them is considered to be sufficiently validated for use as a diagnostic or surrogate parameter for clinical outcome (Turner 2009; Bowser 2011). Diagnosis is mainly clinical and should be based on the revised El Escorial Criteria (EEC) (see Table 1; Brooks 2000).

The introduction of the new Awaji electrodiagnostic algorithm added to the El Escorial criteria seems to improve diagnostic sensitivity with no loss in specificity but its clinical usefulness is still not fully established and is currently under investigation (see Table 2; de Carvalho 2008,2009 and 2012, Schrooten 2011, Dengler 2012).

Only patients with definite or probable ALS according to the modified EE criteria should be included in clinical trials. The use of the modified EEC for diagnosis is still considered to be the gold standard in the clinical trial setting; however refined criteria may increase diagnostic sensitivity in the future. The diagnosis should be confirmed by suitably trained and qualified expert physicians.

5.2. Inclusion and exclusion criteria

The following patients should be excluded from clinical trials in ALS:

- Subjects in whom other causes of neuromuscular weakness have not been excluded
- Subjects with significant cognitive impairment, clinical dementia or psychiatric illness
- Subjects with a diagnosis of neurodegenerative diseases (e.g. Parkinson disease, Alzheimer disease)
- Subjects on other concurrent investigational medications
- Subjects with a significant pulmonary disorder not attributed to ALS or who require treatments that might complicate the evaluation of ALS on respiratory function.

Differences between countries in ALS management and standard of care should be taken into account. For ethical reasons the inclusion of only riluzole naïve patients might not be feasible and stratification/subgroup analysis for riluzole should be undertaken as appropriate for the study design (see section 8.1).

6. Therapeutic Efficacy Measures

6.1. Survival and time to failure analyses

Survival time should normally be a primary endpoint of ALS trials aiming at disease modification. Survival data may be confounded by use of non-assisted ventilation strategies. Use may therefore be made of a time to event endpoint recording time to death, and/or time to tracheostomy and time to permanent continuous ventilator dependence. Criteria for tracheostomy and continuous assisted ventilation dependence as a study endpoint event should be carefully pre-specified and standardized since considerable variability in patient management exists between countries and regions. Where these endpoints are used, an additional analysis using only death as the endpoint should also be provided to allow consideration of the consistency of the results.

6.2. Functional Measures

The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) and the revised version that includes respiratory function (ALSFRS-R) is the most widely used instrument to measure function in ALS clinical trials (see Table 3). It is a validated disease-specific questionnaire (Kaufmann 2007; Maier 2012; Leigh 2004; Cedarbaum 1999).

Functional decline averages about 1 point per month in untreated patients (Castrillo-Viguera 2010).The minimum treatment effect size that could be considered clinically meaningful as outcome in clinical trials should be defined a priori.

Other scales that measure functional disability such as the Norris scale (Norris 1974), the Appel Scale (Appel 1987) and the ALS Severity Scale (ALSSS; Hillel 1989) may also be used (Brooks 2006), however the ALSFRS-R should be the preferred scale. If it is not used as primary endpoint it should at least be secondary.

Assessments of specific activities (e.g. timed walking distance) may be acceptable as secondary variables.

6.3. Muscle strength measurements

Muscle strength (muscle power) will usually be one of the secondary endpoints. Options include simple manual muscle testing using an established scale such as MMT and quantitative muscle testing scores such as hand-held dynamometry (HHD) or the more burdensome fixed dynamometry, and more complex quantified methods such as measurement of Maximum Voluntary Isometric Contraction (MVIC) using a computer controlled strain gauge. Other endpoints for assessing neuromuscular impairment such as handgrip strength and fatigability (maximum handgrip strength and sub-maximum handgrip fatigue) should be considered (Visser 2003; Andres 2012).

Decrease in weight is a potentially useful additional indicator of muscle loss and disease progression. Analysis may need to be stratified according to the use of potentially confounding factors such as percutaneous endoscopic gastrostomy.

6.4. Respiratory function measurements

All trials of ALS should include testing of respiratory function. Measurement of vital capacity (VC)/forced vital capacity (FVC) and other variables by spirometry e.g. peak expiratory flow (PEF), forced expiratory volume in one seconds (FEV1), maximal inspiratory pressure (PImax) should be done according to current standards and methods (Hardiman 2011).

In addition, alternative methods to measure respiratory function such as slow vital capacity (SVC) and respiratory muscle strength such as the Sniff Nasal Inspiratory Pressure (SNIP) measurement and the maximum voluntary ventilation test (MVV) as a measure of strength and endurance of respiratory muscles may be used as secondary endpoints (Shefner 2012).

6.5. Assessment of Health Related Quality of Life

Measurement of Health Related Quality of Life is a valuable measure of therapeutic efficacy, which may be applied as a secondary endpoint in ALS trials. Use as a primary endpoint is not recommended.

The use of a well-known general Quality of Life scale as an additional secondary endpoint should be validated for this category of patients and sensitive to change. Both generic (e.g. SF-36, Sickness Impact Profile [SIP])(Bergner 1981) and specific scales, (e.g. ALS Assessment Questionnaires ALSAQ-40 or ALSQ5) are available which can be combined (e.g. SIP/ALS19) (McGuire 1997, Jenkinson 1999 and 2001, Bromberg 2001). The choice of HR-QoL tool should be justified.

6.6. Global measures

Use of physician's and patient's Clinical Global Impression scale (CGI) are useful general secondary efficacy measures. They may reflect undesirable as well as therapeutic effects.

7. Clincal Pharmacology Studies

7.1. Pharmacokinetics

For guidance on pharmacokinetics reference is made to other relevant guidelines.

7.2. Pharmacodynamics

The proposed mechanism of action of a new compound should be described and discussed in relation to results obtained in non-clinical investigations, e.g. in vitro and/or animal models, although it is acknowledged that their availability is still limited. Nevertheless, non-clinical models can be useful for screening of candidate drugs for ALS. At present the best studied animal model to evaluate candidate drugs is transgenic rodents overexpressing the gene encoding superoxide dismutase 1 (SOD-1) (Gurney 1994; Robertson 2002; Danzeisen 2006; van den Bosch 2011). However, as SOD-1 mutations account only for the hereditary type of ALS the above animal model might have little relevance to human sporadic ALS. For this reason, consideration should be also given to the applicability of other animal models of ALS, which have been recently developed or might become available in the future (examples include but are not limited to models with mutations in TDP-43, C90RF72, EPhA4 etc.; Wegorzewska 2009; De Jesus-Hernandez 2011; Renton 2011; Van Hoecke 2012). Animal data and the appropriateness of the model should be evaluated carefully.

The mechanism of action and PD effect could also be supported by in vitro data in human cells.

7.3. Interactions

In general the Guideline on the Investigation of Drug Interactions should be followed to investigate possible pharmacokinetic and pharmacodynamics interactions between the test drug and any other drug that may be prescribed simultaneously in clinical practice.

8. Clinical Efficacy Studies

8.1. Exploratory studies

The standard approach would be to conduct phase I studies to find the safe doses followed by phase II studies to determine biologic activity before conducting phase III studies to determine efficacy. It is generally preferred to establish dose response in a phase II multiple arm parallel fixed dose study in order to maximize confidence that the dose(s) studied in phase III are optimal. However, it is possible to provide dose response data at least in part from confirmatory phase III trials where dose finding is lacking from phase II, but in any event robust data allowing comparison of at least three doses are necessary to establish a dose response relationship.

The use of motor and respiratory measures in phase II studies as primary endpoints allow a smaller sample size and shorter study duration to show drug effects. Currently the vast majority of phase II ALS trials employ functional endpoints, usually the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (see section 6.2) rather than survival (Gladman 2012). However, this is challenged by the observation that functional outcome and measures of strength often translate poorly into survival endpoints in phase III trials (Lacomblez 1996; Pascuzzi 2010).

8.2. Therapeutic confirmatory studies

8.2.1. Trials for disease modifying treatments

For disease modifying treatments the primary goal is the slowing or even reversal of disease progression. Trials should aim to demonstrate a beneficial effect on both functioning and survival. While future studies may seek to demonstrate efficacy for primary prevention, particularly in familial ALS, clear guidance cannot yet be provided concerning trials with this objective.

Study design and choice of control groups

To assess the effects of medicinal products for treatment of patients with ALS parallel, double blind, randomised placebo controlled trials are necessary. Historical control group data on survival and other key outcome measures instead of a placebo control are not acceptable due to changes in diagnostic criteria, variability of patient populations and evolving changes in standard of care of these patients.

Riluzole is approved for modifying disease progression in ALS and is currently prescribed to the majority of patients. Depending on the mechanism of action new treatments may in principle therefore be developed as an add-on treatment in combination with riluzole (or in the future with another approved disease modifying drug) or as a new monotherapy.

For trials to support an add-on combination therapy indication, patients stabilized on standard treatment (currently this would be riluzole) would be randomized to receive either the new drug or placebo; the trial objective would be to demonstrate superiority to placebo.

For a monotherapy indication there are some ethical issues with placebo controlled trials because of the availability of riluzole. A two arm parallel group placebo controlled trial can however be performed in patients not taking riluzole for reasons unrelated to the trial. A superiority trial versus riluzole would also be satisfactory, while a non-inferiority trial versus riluzole is not recommended. . Superiority trials are preferred in principle to active comparator non-inferiority trials. Alternatively, a placebo controlled trial including patients taking riluzole as well as those not taking disease modifying treatment for reasons unrelated to the trial could provide efficacy data for the new treatment both as add-on to riluzole and as monotherapy. In this case recruitment should be stratified by riluzole use and should aim to achieve sufficient numbers in both categories to achieve sufficient statistical power.

Study duration

Trial duration to show a disease modifying effect should be at least 12 months.

Primary endpoints and methodological considerations

In general two primary endpoints from the domains of disability and survival should be prespecified to estimate slowing of disease progression and increased survival. Important primary efficacy variables in ALS trials are time to death or permanent assisted ventilation and ALSFRS-R (see section 6). Due to the increasing use of non-invasive assisted ventilation strategies and nutritional measures it might be necessary to consider a survival endpoint that incorporates death and other end-of life measures that prolong life in ALS patients (e.g. non-invasive ventilation [NIV], ventilation via tracheostomy).

If alternative strategies are pursued applicants are encouraged to adjust these via scientific advice before starting clinical trials.

8.2.2. Trials for symptomatic treatments

For treatments whose mechanism of action supports the expectation that they may improve symptoms of ALS but would not have a beneficial effect on disease progression, trials should aim to demonstrate a beneficial effect on both symptoms (normally muscle strength) and functioning. Effect on disease progression should still be measured however to exclude a negative effect of treatment. Suitable candidates for development as symptomatic treatments could potentially include products with a direct action on muscles or an effect on neuronal conduction that does not affect the neurodegenerative process and would be expected to be reversible on cessation of treatment. An indication for symptomatic treatment only would generally not be approvable for a product with a mechanism of action indicative of a disease modifying effect but for which benefit on outcome was not shown. Non-specific symptomatic treatments, for example anti-spasticity drugs, would generally not be approvable for a “pseudo-specific” indication for symptomatic treatment of ALS.

Study design and choice of control groups

At present no medicinal product is yet authorized for symptomatic improvement in muscle power and consequent functional improvement (including that related to respiratory muscles). Therefore two arm parallel group placebo controlled trials are currently recommended; the trial objective would be to demonstrate superiority to placebo.

Study duration

Study duration for medicinal products with an effect only on symptomatic improvement (e.g. muscle strength and related function) may in principle be of shorter duration than for products with potential

disease modifying effects. Depending of the mechanism of action pivotal efficacy trials of 3 to 6 months duration could be sufficient. Safety data over 12 months are required to exclude negative impact on disease modifying outcomes (e.g. survival as a key safety outcome). This follow-up allows also to estimate the duration of the symptomatic effect.

Primary endpoints

For products developed for symptomatic treatment muscle strength and function should be the primary endpoints. However, this only holds true for products that by their mechanism of action do not affect the neurodegenerative process and it will be necessary to estimate the extent of the possible adverse effects on disease progression and survival and to discuss this in relation to the clinical relevance of the results.

8.3. General methodological considerations

All patients should receive optimized standard of care in addition to study medication. Details of standard of care and prior and concomitant medication, including use of riluzole and any other ALS treatments, should be documented in detail.

Investigators should be properly trained in evaluation of patients with ALS using the measurement tools employed in the trial. Measures such as inter-rater variability should be documented.

Mental status may be a possible confounding factor as psychological factors have been shown to influence survival. In addition, a number of outcome variables are influenced by mood, particularly voluntary and maximal contraction. Therefore, consideration should be given to the use of an adequate measurement for mood evaluation in clinical trials and to evaluate the impact of these on efficacy outcome.

9. Studies in special populations

Children and adoslescents

ALS only rarely affects children and adolescents and most cases are genetic with a considerable heterogeneity (Turner 2012). Therefore specific studies in this population are not considered to be feasible and are not required. Paediatric patients diagnosed with ALS may be included in the adult studies.

Older Patients

Age of onset is highest in the late fifties and early sixties of patients and these patients will be included in clinical trials. Incidence of ALS over the age of 70 is very rare and due to the low life expectancy (see section 1) no specific studies in the older patients are considered necessary.

10. Safety Evaluations

In general, the ICH E1 Note for guidance on population exposure applies.

Identified adverse events (AE) should be characterized in relation to the duration of treatment, the dose and/or plasma level, the recovery time, age and other relevant variables. Assessment of adverse events, especially those predicted by the pharmacodynamic properties of the investigational product should be performed using a systematic and planned methodology.

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug reactions, drop-outs and patients who died while on therapy. Depending on the substance studied relevant guidelines with specific safety topics should be taken into account.

Certain complications occur more frequently in ALS patients, e.g. thromboembolic events, aspiration pneumonia and malnutrition. They need to be identified and carefully monitored when determining the safety of therapeutics in clinical development.

Definitions

Table 1 Summary of revised El Escorial research diagnostic criteria for ALS (Airlie House 1998)

The diagnosis of ALS requires:
1 Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination;
2 Evidence of UMN degeneration by clinical examination, and
3 Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,
Together with the absence of:
[1] Electrophysiological and pathological evidence of other disease that might explain the signs of LMN and/or UMN degeneration, and
[2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
Categories of clinical diagnostic certainty on clinical criteria alone
Definite ALS
• UMN signs and LMN signs in 3 regions
Probable ALS
• UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs
Probable ALS - Laboratory supported
• UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions
Possible ALS
• UMN signs and LMN signs in 1 region (together), or
• UMN signs in 2 or more regions
• UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs
UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.
LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation.
Regions reflect neuronal pools: bulbar. cervical. thoracic and lumbosacral.

Table 2: Awaji-shima consensus recommendation for the application of electrophysiological tests to the diagnosis of ALS, as applied to the revised El Escorial Criteria (de Carvalho et al. 2008)

1. Principles (from the Airlie House criteria)
The diagnosis of amyotrophic lateral sclerosis [ALS] requires
(A) the presence of

(1) evidence of *lower motor neuron (LMN) degeneration* by clinical, electrophysiological or neuropathological examination

(2) evidence of *upper motor neuron (UMN) degeneration* by clinical examination; *and*

(3) *progressive spread of symptoms or signs* within a region or to other regions, as determined by history, physical examination, or electrophysiological tests

(B) the absence of

(1) *electrophysiological or pathological evidence of other disease processes* that might explain the signs of LMN and/or UMN degeneration, and

(2) *neuroimaging evidence of other disease processes* that might explain the observed clinical and electrophysiological signs

2. Diagnostic categories

Clinically definite ALS is defined by *clinical or electrophysiological* evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions.

Clinically probable ALS is defined on *clinical or electrophysiological* evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs

Clinically possible ALS is defined when *clinical or electrophysiological* signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded

These recommendations emphasize the equivalence of clinical and electrophysiological tests in establishing the neurogenic change in bodily regions. The category of "Clinically Probable laboratory-supported ALS" is rendered redundant.

Table 3: ALS functional Rating Scale – Revised (ALSFRS-R)

Bulbar Function	***Gross Motor Function***
1. Speech 4. Normal speech processes 3. Detectable speech disturbance 2. Intelligible with repeating 1. Speech combined with nonvocal communication 0. Loss of useful speech	**7. Turning in bed** 4. Normal 3. Somewhat slow and clumsy, but no help needed 2. Can turn alone or adjust sheets, but with great difficulty 1. Can initiate, but not turn or adjust sheets alone 0. Helpless
2. Salivation 4. Normal 3. Slight but definite excess of saliva in mouth; may have nighttime drooling 2. Moderately excessive saliva; may have minimal drooling 1. Marked excess of saliva with some drooling 0. Marked drooling; requires constant tissue or handkerchief	**8. Walking** 4. Normal 3. Early ambulation difficulties 2. Walks with assistance 1. Non-ambulatory functional movement only 0. No purposeful leg movement
3. Swallowing 4. Normal eating habits 3. Early eating problems-occasional choking 2. Dietary consistency changes 1. Needs supplemental tube feeding 0. NPO (exclusively parenteral or enteral feeding)	**9. Climbing stairs** 4. Normal 3. Slow 2. Mild unsteadiness or fatigue 1. Needs assistance 0. Cannot do
Fine Motor Function	***Respiratory Function***
4. Handwriting 4. Normal 3. Slow or sloppy; all words are legible 2. Not all words are legible 1. Able to grip pen but unable to write	**10. Dyspnea** 4. None 3. Occurs when walking 2. Occurs with one or more of the following: eating, bathing, dressing (ADL) 1. Occurs at rest, difficulty breathing when either sitting or lying

0. Unable to grip pen	0. Significant difficulty, considering using mechanical respiratory support
5a. Cutting Food 4. Normal 3. Somewhat slow and clumsy, but no help needed 2. Can cut most foods, although clumsy and slow; some help needed 1. Food must be cut by someone, but can still feed slowly 0. Needs to be fed	**11. Orthopnea** 4. None 3. Some difficulty sleeping at night due to shortness of breath. 2. Does not routinely use more than two pillows 1. Needs extra pillow in order to sleep (more than two) 0. Can only sleep sitting up
5b. Alternate Question for Cutting Food for Patients with Gastrostomy 4. Normal 3. Clumsy but able to perform all manipulations independently 2. Some help needed with closures and fasteners 1. Provides minimal assistance to caregiver 0. Unable to perform any aspect of task	**12. Respiratory insufficiency** 4. None 3. Intermittent use of BiPAP 2. Continuous use of BiPAP 1. Continuous use of BiPAP during the night and day 0. Invasive mechanical ventilation by intubation or tracheostomy
6. Dressing and hygiene 4. Normal function 3. Independent and complete self-care with effort or decreased efficiency 2. Intermittent assistance or substitute methods 1. Needs attendant for self-care 0. Total dependence	

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List of Abbrevations

AC: Awaji criteria

ALS: Amyotrophic lateral sclerosis

ALSAQ-40: ALS Assessment Questionnaire 40

ALSFRS/ ALSFRS-R: Amyotrophic lateral sclerosis functional rating scale/ Amyotrophic lateral sclerosis functional rating scale revised

ALSSS: ALS Severity Scale

CGI: Clinical global impression scale

EEC: El Escorial Criteria

FALS: Familial amyotrophic lateral sclerosis

FEV1: Forced expiratory volume in one second

FVC: Forced vital capacity

HHD: Hand-held dynamometry

JALS: Juvenile Amyotrophic Lateral Sclerosis

LMN: lower motor neuron

MMT: Manual muscle testing

MMV: Maximum voluntary ventilation

MVIC: Maximum voluntary isometric contraction

PEF: peak expiratory flow

PImax: maximal inspiratory pressure

SALS: Sporadic amyotrophic lateral sclerosis

SIP: Sickness impact profile

SNIP: Sniff nasal inspiratory pressure

SOD-1: Superoxide Dismutase 1

SVC: Slow vital capacity

UMN: upper motor neuron

VC: Vital capacity