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

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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).

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[1] Editorial corrections.

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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.

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, mitochondrial dysfunction, changes in intracellular calcium levels, glutamate excitoxicity and genetic factors (Guerney 1994; Leigh 2004). A growing number of ALS-associated genes have been identified recently and are now under investigation to provide more insight in the aetiology of the disease (Deng 2012; Al-Chalabi 2012; Ticozzi 2011; Volonté 2015). There is clinical, pathological and genetic overlap between ALS and other progressive neurodegenerative syndromes such as frontotemporal dementia (FTD) (DeJesus-Hernandez 2011; Orr 2011; Pratt 2012; Ludolph 2012; Phukan 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). Identification of *C9orf72* repeat expansions in patients without family history of ALS challenges the traditional division between familial and sporadic disease (Turner 2013, Rohrer 2015). Although FALS is clinically and genetically heterogeneous (Chen 2004, Cooper-Knock 2012, Leblond 2014), the clinical presentation of FALS and SALS is very similar. In most cases, disease onset is during late adulthood, but juvenile (prior to 25 years of age) and “young-onset” ALS cases (prior to 45 years), respectively represent approximately 1 and 10% of all cases (Kiernan 2011; Turner 2012; Aggarwal 2006; Zou 2013; Chance 1998; Rabin 1999; Orban 2007; Belzil 2012; Gouveia 2007; Bäumer 2010). The mean age for typical ALS disease onset (adult-onset) is estimated at 61.8 ± 3.8 years (range 54-67 years) (Chio 2013; Leblond 2014). Incidence decreases rapidly after 80 years of age (Logroscino 2010).

In sporadic ALS men are more commonly affected than women (1.4-2.5:1) although the number of women affected increases with increasing age. Median survival time is about 2-3 years; however, about 20% of patients may survive longer than 5 years and a small percentage even longer than 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). ALS is associated with fronto-temporal dementia (FTD) in about 14% of incident cases and a further 30% have evidence of cognitive impairment without dementia (Byrne 2012; Turner 2013). Cognitive impairment attributed to abnormalities in frontal lobe function including executive dysfunction comprises an important component of the clinical phenotype not only in patients with comorbid FTD (see also section 6.7) (Strong 2009; Phukan 2012). The presence of the *C9orf72* hexanucleotide repeat expansion is a strong predictor of cognitive and behavioural impairment associated with ALS (Byrne 2012; Cooper-Knock 2012; Bede 2013)

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. In patients without dementia, executive dysfunction is an important negative prognostic indicator (Elamin 2011, 2013).

Riluzole is the only approved medication for modifying disease progression in ALS and apart from that treatment is mainly palliative (Miller 2009; EFNS guideline 2012).

2. Scope

This Guideline is intended to provide guidance on the clinical investigation of drugs for the treatment of ALS. Primary lateral sclerosis with pure UMN involvement and progressive muscular atrophy with pure LMN involvement are not within the scope of this guideline. The guideline focuses on treatment aimed to modify disease progression. In addition, some guidance is given on drugs for symptomatic treatment of muscle strength. The guideline has taken account of the most up-to-date research data and data from clinical trials in ALS. 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 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 of a product 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. Non-specific symptomatic treatments (e.g. drooling or pseudobulbar affect) are not within the scope of this guideline (see section 8.2.2). Studies should be randomised, 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 of disease progression
- Improvement of symptoms of ALS, e.g. muscle strength and related function.

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 to support 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. Inclusion criteria and diagnosis

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 recognised until considerable motor function has been lost and the mean delay from presentation to diagnosis is approximately 1 year (Mitchell 2010; Bowser 2011). Diagnosis of ALS may be straightforward if the patient presents with progressive, generalised 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, e.g. bulbar signs and time from first symptom to diagnosis (Beghi 2011), and concomitant use of riluzole (see section 8.2.1).

Several candidate protein-based, neurophysiological and neuroimaging biomarkers for ALS have been identified but until now none has been 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 EEC 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; Chen 2010; Schrooten 2011; Dengler 2012).

Patients with a diagnosis of definite, probable or possible ALS are eligible for inclusion in clinical trials. The use of the modified EEC for diagnosis is considered the gold standard in the clinical-trial setting; however refined criteria may increase diagnostic sensitivity in the future (Traynor 2000; Turner 2013). The diagnosis should be confirmed by suitably trained and qualified expert physicians. Validated prognostic models may be used to stratify the study population by predicted rates of progression (Gomeni 2014).

5.2. Exclusion criteria

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

- Subjects with other causes of neuromuscular weakness
- Subjects with severe active psychiatric illness
- Subjects with a diagnosis of another neurodegenerative disease (e.g. Parkinson disease, Alzheimer's 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 the effect 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 sections 5.1 and 8.1).

6. Therapeutic Efficacy Measures

6.1. Survival and time to failure analyses

Survival time should normally be an endpoint of ALS trials aiming at disease modification. If it is not used as primary endpoint it should at least be secondary (see section 8.2).

Survival data may be confounded by use of ventilation strategies. Use may therefore be made of a composite time-to- event endpoint recording time to death, tracheostomy or permanent continuous ventilator dependence whatever occurs first. Criteria for tracheostomy and continuous assisted

ventilation dependence as a study endpoint event should be carefully pre-specified and standardised since patient management varies considerably between countries and regions. Where these endpoints are used, an additional analysis using only time to death as the endpoint should also be provided to allow evaluation 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).

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) were previously used (Brooks 2006); however, the ALSFRS-R is the preferred scale. If it is not used as primary endpoint it should at least be a secondary one. If a newly developed and validated measure of function is used as endpoint, a rationale for its use should be given (Franchignoni 2013).

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 manual muscle testing (MMT) and quantitative muscle testing scores such as hand-held dynamometry (HHD) or 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 second (FEV1), maximal inspiratory pressure (PImax) should conform with 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. The choice of HR-QoL tool should be justified.

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 should be sensitive to change. Both generic (e.g. SF-36, EQ5-D, the Health Utilities Index [HUI], 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).

6.6. Global measures

The physician's and patient's Clinical Global Impression scales (CGI) are useful general secondary efficacy measures. They may reflect undesirable as well as therapeutic effects. In addition, the CGI may be useful in anchor-based assessments of clinically meaningful change.

6.7. Additional endpoints

Electrophysiological assessments

More advanced electrophysiological assessments such as MUNE (motor unit number estimation) or MUNIX (motor unit number index) may be helpful in phase II trials to determine target activity and may be used as secondary outcome in phase III trials in addition to muscle strength measurements to provide insight into the mechanism of action (Shefner 2011, Neuwirth 2015, Rutkove 2015).

Staging of disease progression

Inclusion of concepts related to the development, validation and implementation of a staging system for ALS disease progression that partitions patients into meaningful groups based on levels of functionality (e.g. regionally limited disease, loss-of independence, tracheostomy dependent) may be considered (Roche 2012). Staging can be used as a complementary measure to the ALSFRS-R to provide additional information about a patient´s disease burden during the course of a clinical trial (Chiò 2015; Balendra 2015).

Cognitive functioning

Cognitive changes in ALS patients are most accurately evaluated through neuropsychological assessment. This involves the systematic administration of cognitive tests which characterise different areas of thinking including attention, language, memory, visual-spatial processing and executive functioning. Change in declining cognitive status may be considered as an important secondary outcome; however, currently there is no standardised battery of tests for the assessment of cognition in ALS (Strong 2009; Phukan 2012).

7. Clinical 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 may still be limited. Nevertheless, non-clinical models can be useful for screening 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 this 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, FUS/TLS, 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 (Ludolph 2010).

The mechanism of action and PD effect could also be supported by in vitro data in human cells (Dimos 2008; Coatti 2015).

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 likely to 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 biological activity and establish dose response before conducting phase III studies to determine efficacy. In certain circumstances it may be appropriate to conduct phase I studies in ALS patients, such as when the target mechanism is not expressed in healthy subjects. It is generally preferred to estimate the dose response relationship in a phase II multiple arm parallel fixed dose study in order to maximise confidence that the dose(s) studied in phase III are optimal. Depending on the active substance, identification of the highest tolerated dose might not always be possible. The use of pharmacokinetic/pharmacodynamics data to assist dose selection is encouraged. Drug exposure coupled with levels of target engagement can enable a more efficient exploration of the dose-/exposure-response curve. This approach can be further enhanced by PK/PD modelling and simulation, and incorporation of biomarker and/or surrogate marker data once available. However, it is also possible to provide dose-response data at least in part from confirmatory phase III trials where dose finding is lacking from phase II.

The use of motor and respiratory measures in phase II studies as primary endpoints allow for a smaller sample size and shorter study duration to show a drug effect. 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) (Gladman 2012).

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 address the effect on both, functioning and survival (see below). 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 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. In addition to general reasons related to the inadequacy of historical controls to establish a causal relation, historical controls are prone to confounding effects, e.g. changes in diagnostic criteria, variability of patient populations and evolving changes in standard of care and thus outcome 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 a) an add-on treatment in combination with riluzole (or in the future with another approved disease modifying drug) or as b) new monotherapy.

a) For trials to support an add-on combination therapy indication, patients stabilised on standard treatment (currently this would be riluzole) would be randomised to receive either the new drug or placebo; the trial objective would be to demonstrate superiority to placebo. In case there are patients ineligible to riluzole use for reasons unrelated to the trial, randomisation should be stratified by riluzole use.

b) Another option is a monotherapy trial versus riluzole as active comparator. In this case superiority should be demonstrated while a non-inferiority trial versus riluzole is not acceptable as proof of efficacy due to concerns over assay sensitivity.

Study duration

Trial duration depends on the expected rate of progression which in turn depends on the population included. Study duration of 12-18 months may be sufficient. However, it is recommended to check during the trial whether the progression rates are in accordance with the assumptions. Such a blinded interim analysis should only be used for sample size re-estimation if necessary but not for stopping the trial for efficacy. Appropriate measurements should be implemented to assure non-contamination of study blinding and other elements related to the study integrity and validity.

Moreover, an extended follow-up may be needed to generate further survival data (see section on endpoints and methodological considerations below).

Efficacy endpoints and methodological considerations

A response criterion that could be considered a clinically meaningful outcome in clinical trials should be defined and justified a priori. In general endpoints from the domains of disability and survival should be pre-specified to estimate slowing of disease progression and increased survival. As primary efficacy variable in ALS trials can use either time to death including other end of life measures that prolong life in ALS patients (e.g. non-invasive ventilation [NIV], ventilation via tracheostomy) or function (ALSFRS-R) (see section 6), or both. For proof of efficacy a clear and significant effect on one domain and a trend on the other may be sufficient. The choice of primary endpoint should not lead to insufficient data for assessing the effect on survival.

Alternatively, other primary endpoints might be considered such as a time-to-event endpoint with the event defined as death or a predefined deterioration on the ALSFRS-R scale or a composite endpoint of survival and functioning (Finkelstein 1999; Berry 2013; Cudkowicz 2013). In this case the overall results should not be driven by a change in one or the other but on both.

Since high or relevant mortality rates are expected in these trials, an analysis of score data such as functioning at study end in survivors only may result in relevant selection bias and interpretational issues. This has to be discussed and to some extent might be accounted for by sensitivity analyses.

Alternative study designs such as delayed start design trials could be considered to differentiate a disease modifying from a symptomatic effect.

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 and related function

For treatments whose mechanisms of action are expected to 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 (muscle strength) and functioning. 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. Effect on disease progression should still be measured however to exclude a negative effect of treatment. 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 authorised 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. Since most patients will be on riluzole treatment either an add-on design on top of riluzole or a stratification by riluzole use should be undertaken.

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).

Efficacy endpoints

For products developed for symptomatic treatment, muscle strength and function are considered the most important endpoints and should show consistency in effects. According to the expected effect, one should be selected as primary endpoint and the other as secondary endpoint. 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 optimal 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.

Cognitive 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 evaluation of mood and cognitive function in clinical trials and to evaluate the impact of these on efficacy outcome.

9. Studies in special populations

Children and adolescents

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

Older Patients

Mean age of onset is in the early sixties and these patients are most likely to be included in clinical trials. The ALS incidence is highest at older ages (60 to 75 years). Thus efforts should be made to recruit patients > 65 years and where possible > 75 years of age in the therapeutic confirmatory studies to assess both efficacy and safety in these groups (Logroscino 2010, Chio 2013).

10. Safety Evaluations

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

Identified adverse events (AE) should be characterised 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) (Wijesekera et al. 2009 according to Brooks et al 2000)

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

LMN (lower motor neuron) signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation.
UMN (upper motor neuron) signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.
Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

The category 'suspected ALS' has been deleted from the revised El Escorial criteria.

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 emphasise 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) (Cedarbaum 1999)

Bulbar Function	***Gross Motor Function***
1. Speech	**7. Turning in bed**
4. Normal speech processes	4. Normal
3. Detectable speech disturbance	3. Somewhat slow and clumsy, but no help needed
2. Intelligible with repeating	2. Can turn alone or adjust sheets, but with great difficulty
1. Speech combined with nonvocal communication	1. Can initiate, but not turn or adjust sheets alone
0. Loss of useful speech	0. Helpless
2. Salivation	**8. Walking**
4. Normal	4. Normal
3. Slight but definite excess of saliva in mouth; may have nighttime drooling	3. Early ambulation difficulties
2. Moderately excessive saliva; may have minimal drooling	2. Walks with assistance
1. Marked excess of saliva with some drooling	1. Non-ambulatory functional movement only
0. Marked drooling; requires constant tissue or handkerchief	0. No purposeful leg movement
3. Swallowing	**9. Climbing stairs**
4. Normal eating habits	4. Normal
3. Early eating problems-occasional choking	3. Slow
2. Dietary consistency changes	2. Mild unsteadiness or fatigue
1. Needs supplemental tube feeding	1. Needs assistance
0. NPO (exclusively parenteral or enteral feeding)	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 0. Unable to grip pen	**10. Dyspnoea** 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. 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. Orthopnoea** 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 bi-level positive airway pressure (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 Abbreviations

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

BiPAP: Bi-level positive airway pressure

CGI: Clinical global impression scale

C9orf72: Chromosome 9 open reading frame 72

EEC: El Escorial Criteria

FALS: Familial amyotrophic lateral sclerosis

FEV1: Forced expiratory volume in one second

FTD: Fronto-temporal dementia

FUS/TLS: Fused in sarcoma/translated in liposarcoma

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

MUNE: Motor unit number estimation

MUNIX: Motor unit number index

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

TDP-43: TAR DNA-binding protein

UMN: upper motor neuron

VC: Vital capacity