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POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

These notes are intended to provide guidance in the evaluation of drugs for the treatment of Amyotrophic lateral sclerosis (ALS).

They should be read in conjunction with current and future EC Directives and CPMP and ICH guidelines.

It should be noted that research in the area of treatments for ALS is at an early stage with the potential for rapid changes and developments. These points to consider are intended to be applied with flexibility, and should not be considered as a final and complete view of this topic.

I. INTRODUCTION

Amyotrophic lateral sclerosis is a motor neuron disease. It is characterised by degeneration and loss of upper and lower motor neurons. Motor neuron loss is progressive and prognosis is poor.

Incidence rate estimates of ALS range from 0.8-2.4 per 100,000 persons per year. At disease onset most patients are more than 40 years old and the incidence increases with age. Median survival time is about 2-3 years. Death is usually due to respiratory failure. About 20% of patients may be alive after 5 years and 6% after 10 years. 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.

The aetiology of ALS is unknown. Most cases are sporadic (SALS), although about 5% are inherited in an autosomal dominant manner as familial ALS (FALS).

II. DIAGNOSTIC CRITERIA OF ALS

The "EL Escorial" diagnostic criteria of ALS require presence of:

- evidence of lower motor neuron (LMN) damage by clinical, electrophysiological or neurophysiological examination,
- evidence of upper motor neuron (UMN) damage by clinical examination, and
- progressive spread of symptoms or signs together with the absence of:
  - electrophysiological and pathological evidence for other disease processes that might explain these LMN/UMN signs, and
  - neuroimaging evidence of other disease processes that might explain the observed signs

According to these criteria, the diagnosis of *definite ALS* is made on clinical grounds only by the presence of upper and lower motor neuron signs (UMN and LMN, respectively) in the bulbar region and at least two other spinal regions (cervical, thoracic, lumbosacral) or by the presence of UMN and LMN signs in three spinal regions.

Probable ALS is defined on clinical grounds alone by the presence of upper and lower motor neuron signs in at least two regions. Moreover, some upper motor neuron signs must be rostral from the lower motor neuron signs.

Probable ALS - laboratory supported is defined on clinical ground by the presence of UMN and LMN signs in one region or UMN in one region with EMG evidence for LMN signs in 2 limbs, and proper application of neuroimaging and other laboratory techniques to exclude other diseases.

Possible ALS is defined by the presence of upper and lower motor neuron signs in one region, or upper motor neuron signs in two or three regions.

Suspected ALS can be diagnosed when lower motor neuron signs are present in two or three regions.

III. STUDY OBJECTIVES

The following study objectives could be considered:

1. improvement of symptoms of ALS
2. increased survival
3. delay or stabilisation of disease progression (including prevention of disease onset and spread of disease to previously unaffected areas)
4. improvement in quality of life or reduction of the rate of deterioration of quality of life

Very few studies have attempted to address the last group of objectives (see VIII.5).

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.

IV. STUDY POPULATION

Use of the WNF El Escorial diagnostic criteria is acceptable. It is anticipated that most trials will include patients categorised as definite or probable ALS. Consideration may be given to inclusion of patients with a diagnosis of possible ALS. The study population in most trials of ALS may include patients with both sporadic and familial ALS.

Prognostic factors include bulbar signs at entry, duration of disease at entry, rate of progession before entry in the trial, familial or sporadic disease and baseline values of muscle strength, spasticity, ventilatory function, weight and severity (global scale). The heterogeneity of the study population (probable or definite ALS, familial or sporadic disease) and prognostic factors should be taken into account in trial design and analysis of the results. Trials will usually include patients with different prognostic factors and rates of progression, and may include patients with both sporadic and familial ALS.

V. STUDY DESIGN

Randomised, double-blind, parallel-group trials are essential for the proper investigation of products for treatment of ALS. At present the new drug must be superior to placebo, or if placebo is not used, superior to an authorised product. Trial duration should be at least 12 months.

Care should be taken to ensure that follow-up of patients is as complete as possible for as many patients as possible, even after the discontinuation of treatment.

The number of required patients will vary with the type of study, stage of disease in the study population, significance level desired, power of the study, assumed difference between drug and placebo group, and drop-out rate expected.

Ideally it is desirable to avoid any concomitant medication which might impair mental or physical functioning. However use of many such agents, including hypnotics, antidepressants, anticholinergics, etc., may be unavoidable in patients with ALS. Consideration should be given to including in the trial protocol an acceptable standard agent and dosage level for such agents which are likely to be prescribed. Concomitant medication which may have an impact on efficacy should be summarised by randomised treatment group and its impact discussed.

In accordance with the ICH E9 Guideline on Statistical Principles for Clinical Trials (CPMP/ICH/363/96), study designs may be stratified to avoid imbalance in prognostic variables. Alternatively, stratification of analysis may eliminate or reduce the impact of any imbalance on outcome.

VI. INCLUSION AND EXCLUSION CRITERIA

Most trials of ALS therapies have been conducted in patients aged 18 - 85, and with evidence of disease progression for between 6 months and 5 years. It should be noted that there are no regulatory requirements for trial patients to be specifically restricted to these groups. Patients with significant sensory abnormalities, dementia, other neurologic diseases, uncompensated medical illness, substance abuse and psychiatric illness must be excluded. Patients must not be on concurrent investigational medication.

Patients with pre-existing pulmonary disorders not attributed to the ALS should be excluded. Consideration should be given to the use of a minimum standard of respiratory function as an exclusion criteria (e.g. FVC) to reduce the drop-out rate throughout the trial.

VII. EFFICACY VARIABLES

Important primary efficacy variables in ALS trials are change in muscle strength from baseline, disability, and survival. Time to death, and/or time to tracheostomy and/or time to permanent continuous ventilator dependence may be the primary efficacy parameter, provided that the criteria for tracheostomy and continuous ventilator dependence are carefully pre-specified.

In the pivotal trials it is recommended that two primary endpoints should be pre-specified from the domains of survival, disability and muscle strength. When survival is not a primary endpoint, it will be necessary to estimate the extent of the possible adverse effect on mortality shown by the available data and to discuss this in relation to the clinical relevance of results.

VIII. METHODS OF EFFICACY VARIABLES MEASUREMENT

1. Survival and time to failure analysis

Survival time will usually be one of the primary endpoints of ALS trials. Use may be made of a composite time to event endpoint recording time to death, and/or time to tracheostomy, and/or time to permanent continuous ventilator dependence. Criteria for tracheostomy and continuous ventilator dependence should be carefully pre-specified.

Where this is done, an additional analysis using only death as the endpoint should also be provided to allow consideration of the consistency of the results.

2. Muscle strength measurements

Muscle strength (in fact muscle power) is an important variable, and will usually be one of the primary variables. Options include simple manual testing using an established scale, and more complex quantified methods such as measurement of Maximum Voluntary Isometric Contraction (MVIC) using a computer controlled strain gauge. About half of the body mass is muscle. Decrease in weight is a possible alternative secondary variable, which may be considered as a simple estimate of muscle loss and disease progression.

3. Respiratory function measurement

All trials of ALS should include testing of respiratory function. It may be acceptable to include this as one of the primary efficacy variables. Measurement of vital capacity and other variables by spirometry should be done to current standards and methods. FVC and VC are alternatives, ideally both should be measured. Alternative methods to measure respiratory function may be used.

4. Function Tests (Assessment of Disability)

Efficacy variables should include functional tests of disability. These may be rating scales or functional tests (timed or quantitative testing of specific activities). Rating scales should be validated for ALS. Examples include the ALS Functional Rating Scale (ALSFRS), the Baylor ALS Rating Scale, the ALS Severity Scale (ALSSS) and the Norris score.

Use of a physicians Clinical Global Impression scale (CGI) or assessments of specific activities (e.g. timed walking distance) may also be acceptable as secondary variables.

Testing of bulbar function will usually be included in patient assessments. This may be part of the overall function scale used.

5. Assessment of Quality of Life

Measurement of Quality of Life is a valuable and independent measure of therapeutic efficacy, which may be applied as a secondary variable in ALS trials. Use as a primary variable is not recommended. Quality of Life scales specific to ALS have not been developed, and the use of a well-known general Quality of Life scale as an additional secondary variable should be validated for this category of patients.

6. Assessment of mental status

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 to recognise the impact of mood on other variables. Such variables should be considered as secondary.

IX. SAFETY ISSUES

To date no ALS-specific issues have been identified in clinical trials. All usual general principles and issues will apply (see other guidelines).

X. GENERAL DEVELOPMENT STRATEGY

1. Pharmacodynamics

There exist no appropriate animal models of ALS which can be used to test the effect of a new agent on pathophysiological events leading to motor neuron degeneration in man.

2. Pharmacokinetics

No specific requirements for medicinal products for use in ALS have been identified. (The general guideline on pharmacokinetic studies in man will be applicable.)

3. Phases of ALS trials

Clinical development of therapeutic agents for ALS is likely to follow the conventional plan described as Phases I-III. Advice in this document will be most relevant for the planning of pivotal phase III trials.

At present there are no useful surrogate efficacy variables for use in phase II studies. In this situation it is possible that dose response data may be provided from confirmatory phase III trials.