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Committee for Medicinal Product for Human Use (CHMP)

Concept paper on the need for revision of the points to consider on clinical investigation of medicinal products for the treatment of Amyotrophic Lateral Sclerosis

Agreed by CNS Working Party	February 2012
Adoption by CHMP for release for consultation	15 March 2012
Start of public consultation	01 April 2012
End of consultation (deadline for comments)	30 June 2012

The proposed guideline will replace 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	*CHMP, EMA, Concept Paper, Amyotrophic Lateral Sclerosis (ALS)*

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare progressive motor neuron disease (reported incidence 0.8-2.4 per 100 000 person per year) characterised by axonal degeneration and death of motor neurons leading to progressive denervation and atrophy of skeletal muscles, paralysis and in the majority of cases death.

Until now riluzole is the only approved medication for the treatment of ALS. The majority of ALS patients in Europe and more than half of those in the US take riluzole (1,2). Clinical studies with riluzole have demonstrated that the average survival time for patients tested with riluzole was 2-3 months longer than that for patients who received placebo but that riluzole had no effect on disability, muscle strength or other symptoms of ALS (Rilutek SmPC).

ALS therefore still presents an unmet medical need for improvement of symptoms and increased survival.

2. Problem statement

Recently a number of scientific advice procedures have been requested for development programs on medicinal products for treatment of ALS indicating that there is a need for guidance on clinically relevant endpoints to be used in clinical trials and the most appropriate trial design. Clarification was especially needed on the weighting of primary and secondary endpoints given in the whole concept of relevant treatment effects in ALS and the clinical relevance of functional/disability endpoints.

3. Discussion (on the problem statement)

The following critical aspects should be discussed in the update of the guidance document:

- Definition of population;
- Role of comparators in controlled trials;

  Recent study protocols have foreseen placebo control and add-on to riluzole (for ethical reasons) or stratification according to riluzole therapy since riluzole use is different in US and Europe. There is a need to address more clearly the situation where add-on treatment with riluzole isn´t an option (for safety or mechanistic reasons). In particular the role of placebo-controlled trials has to be critically evaluated in the light of upcoming therapies that might have increased effects on survival.
- Choice of outcome parameters and their weighting as (co)primary and secondary efficacy variables;
- Role of functional tests of disability, e.g. ALSFRS and their potential use as surrogate for survival;
- Definition of clinical relevant effects in functional outcome parameters;
- Design of long term efficacy and safety studies.

4. Recommendation

In conclusion, it is recommended to update the current Points to Consider on clinical Investigation of Medicinal Products for the Treatment of Amyotrophic Lateral Sclerosis. Although the key issues of

guidance have not changed and are still valid, in some points more elaborate recommendations could be given. Clearer recommendations are especially needed on the weighting of primary and secondary endpoints in the whole concept of relevant treatment effects in ALS and the clinical relevance of functional/disability endpoints.

5. Proposed timetable

It is planned to release for consultation a draft CHMP guidance document not later than Q1/2 2013.

6. Resource requirements for preparation

The preparation of this guideline will involve the CNSWP. Drafts of the document will be discussed with BSWP, SAWP and other relevant WPs and committees.

7. Impact assessment (anticipated)

It is aimed that the "Guideline on the development of new products for the treatment of Amyotrophic Lateral Sclerosis (ALS)" will be helpful to achieve consensus in the evaluation of such products by regulatory authorities in the European Community. Furthermore, it is expected, that such guideline will provide guidance with respect to methodology, assessment tools and clinically relevant outcomes in ALS and thus would improve quality and comparability of development programs for this specific indication by pharmaceutical companies.

8. Interested parties

The interested parties in the guidance document include learned societies and academia (e.g. Deutsche Gesellschaft für Neurologie (DGN); European Neurological Society (ENS); ALS association and others), pharmaceutical industry (e.g. EFPIA and others) and other regulatory agencies.

9. References to literature, guidelines, etc.

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2. Walley T, Neuropsychotherapeutics in the UK, CNS Drugs 2004;18 (1) 1-12.
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