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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis

Agreed by CNS Working Party	18 December 2025
Adopted by CHMP for release for consultation	16 March 2026
Start of public consultation	31 March 2026
End of consultation (deadline for comments)	30 September 2026

The proposed guideline will replace the Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (EMA/531686/2015, Corr.1, 19 November 2015).

Comments should be provided using this EUsurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Amyotrophic lateral sclerosis, Motor neuron disease, Confirmatory trials

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1. Introduction

Motor neuron disease (MND) covers a heterogeneous group of neurodegenerative disorders characterized by the loss of upper and/or lower motor neurons.

The most common disease is amyotrophic lateral sclerosis (ALS). Typical symptoms are proceeding and spreading of flaccid and/or spastic paresis in skeletal muscles in the extremities, trunk, tongue and throat leading to escalating difficulties in walking, arm/hand utility, breathing and swallowing. Reduction of cognitive functions can be found in around 30-50% of the patients. Some patients develop a frontotemporal dementia. In the pan-European, population-based PRECISION-ALS cohort, the observed median time from onset to death was 2.69 years (interquartile range 1.74-4.34)[1]. Death is typically caused by respiratory insufficiency.

The reported incidence of ALS varies from 0.3-2.5 per 100 000 persons per year. ALS typically affects adults. Juvenile ALS – with onset below 25 years – is extremely rare with a prevalence lower than 1 per million (Orphanet)[2]. The exact aetiology of ALS is still uncertain. Pathophysiologically, ALS is the result of the interplay of a complex interaction between genetic and molecular pathways[3-5]. Progressive upper and lower motor neuron damage and death have been attributed to oxidative damage, mitochondrial dysfunction, changes in intracellular calcium levels, glutamate excitotoxicity protein misfolding and aggregation[6-8]. ALS is considered a proteinopathy and in the vast majority of the patients, a TAR DNA-binding protein 43 (TDP-43) proteinopathy is identified[9]. However, aggregates of other proteins have also been identified in other patients. Indeed, knowledge on the genetics of ALS is rapidly expanding leading to further understanding on the role of certain genetic mutations in shaping pathophysiology and disease heterogeneity of both familial ALS (fALS) and sporadic ALS (sALS). To date at least 40 genes have been identified to have a role in ALS including mutations in *C9orf72*, superoxide dismutase 1 (SOD1), TDP-43, and fused in sarcoma (FUS). Importantly, the implications of genetics in ALS goes beyond pathogenesis and diagnosis/stratification as these mutations may serve as targets for the development of new gene-specific therapies[10].

Diagnostic criteria have evolved since 1994 when the El Escorial criteria (EEC) were agreed[11]. Updates (EEC revised[12] and Awaji criteria[13]) have been developed to increase sensitivity. The most recent update in this serial development of diagnostic criteria is the Gold Coast criteria (GCC)[14]. The GCC has simplified how the diagnosis can be established, describing a single clinical diagnostic entity rather than different disease categories. This may be of value in clinical trials as the utilisation of the so called definite, or definite and probable ALS categories have reduced inclusion rates leading to impaired external validity of clinical trials[15]. Biomarkers have received more attention lately but validation of these is lagging.

Progression of muscular weakness is seen in all ALS-patients but the course varies widely and depends on several factors including site of onset and on the succeeding progression rate. The most widely used functional rating scale is ALS functional rating scale (revised)(ALSFRS-R) but it has some limitations. In the recent years, there have been efforts to overcome some of these limitations[16] and to develop new scales[17].

At present, only two medicinal products have been authorised in the European Union for the treatment of ALS in adults. One of them is authorised in the small subset of patients with a mutation in the SOD1 gene. Thus, there remains an unmet medical need for efficacious and safe treatments for ALS.

Guidance on the clinical investigation of medicinal products in the treatment of other MND are not in the scope of this guidance.

The current ALS guideline (EMA/531686/2015, Corr.1) came into effect in June 2016[18].

2. Problem statement

The current guideline predates some recent developments in the field. Since the first version, new diagnostic criteria and tools for patient phenotyping have been developed. Additionally, the standard of care has evolved with differences in the authorisation of certain medicinal products in the EU and outside the EU, aspects that could impact the design of studies. Further, based on recent regulatory experience, the guidance should be updated on several methodological aspects on the design of efficacy studies in ALS (see below). Finally, the current guideline does not discuss the potential role of biomarkers in the drug development in ALS.

3. Discussion (on the problem statement)

The following critical aspects should be considered to be addressed in the update of the guidance document:

- The new GCC criteria[14], since they have potential implications on both the definition of the target population and on the eligibility criteria for clinical trials.
- Recommendations on eligibility criteria and stratification factors for study populations to reduce exclusion rates, increase external validity, and facilitate homogeneity in trial endpoints.
- The evolution in the standard of care.
- Update recommendations on therapeutic efficacy measures including definitions of death equivalents, global, respiratory and cognitive function measurements.
- The use of biomarkers in ALS with particular emphasis on the use of plasma and cerebrospinal fluid neurofilament protein levels in trials as enrichment marker, stratification tool, efficacy outcome measure.
- Clinical efficacy studies
    - Exploratory studies: update on design aspects including study population, acceptable duration of the trial, acceptable endpoints.
    - Confirmatory studies for medicinal products targeting the underlying disease pathophysiological mechanism(s).
        - Trial design considerations in the context of global variability in the standard of care and an evolving therapeutic landscape (e.g. selection of control, stratification, considerations for combined treatments).
        - Duration of a trial to allow capturing clinically relevant effects in function and survival.
        - Considerations on endpoints using ALSFRS-R tool (e.g. ALSFRS-R adjusted for mortality using the joint modelling approach, Combined Assessment of Function and Survival (CAFS), ALSFRS-R slope analysis).
        - Considerations on definition of estimands, missingness patterns and imputation methods.
        - Considerations on the use of adaptive designs and platforms trials.

- Trial design considerations for Amyotrophic lateral sclerosis - frontotemporal spectrum disorder [19].

The focus on the above aspects is expected to have an influence on the structure and the content of other sections in the guideline.

4. Recommendation

The Central Nervous System Working Party (CNSWP) recommends drafting a revision of the guideline on Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis taking into account the issues identified above.

5. Proposed timetable

It is planned to release for consultation a draft CHMP guidance document not later than Q1 2027.

6. Resource requirements for preparation

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

7. Impact assessment (anticipated)

It is aimed that this guideline will be helpful to achieve a high-level consensus in the evaluation and standardisation of the clinical development plan for medicinal products for the treatment of ALS, enhancing drug development in this condition with large unmet medical need.

8. Interested parties

The interested parties in the guidance document include:

- Learned societies and academia including European Academy of Neurology (EAN), European Network to cure ALS (ENCALS), European Reference Network for Rare Neuromuscular Diseases (ERN-NMD), Treatment Research Initiative to cure ALS (TRICALS), European Pooled ALS data (EUpALS), European College of Neuropsychopharmacology (ECNP)
- Patient's organisations including European ALS Alliance (EALSA), EURORDIS-Rare diseases Europe, European Federation of Neurological Associations (EFNA).
- Other regulatory bodies.

9. References to literature, guidelines, etc.

1. Caravaca Puchades A, McDonough HE, Al-Chalabi A, Chiò A, Corcia P, Galvin M, Hardiman O, Heverin M, Hobin F, Holmdahl O, Ingre C, Lamaire N, Mac Domhnaill É, Manera U, McFarlane R, Mouzouri M, Ombelet F, Opie-Martin S, Sennfält S, Terrafeta Pastor C, Veldink JH, Van Damme P, van den Berg L, van Eijk RPA, Vasta R, Weemering DN, Shaw P, McDermott CJ, Povedano Panadés M. Mapping the natural history of amyotrophic lateral sclerosis: time-to-event analysis of clinical milestones in the pan-European, population-based PRECISION-ALS cohort. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26(sup1):8-19.

2. Orphanet: Juvenile amyotrophic lateral sclerosis. https://www.orpha.net/en/disease/detail/300605 (accessed Feb 16, 2026).

3. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC. Amyotrophic lateral sclerosis. Lancet. 2011 Mar 12;377(9769):942-55. doi: 10.1016/S0140-6736(10)61156-7.

4. Pratt AJ, Getzoff ED, Perry JJ. Amyotrophic lateral sclerosis: update and new developments. Degener Neurol Neuromuscul Dis. 2012 Feb;2012(2):1-14. doi: 10.2147/DNND.S19803.

5. Rizea RE, Corlatescu AD, Costin HP, Dumitru A, Ciurea AV. Understanding Amyotrophic Lateral Sclerosis: Pathophysiology, Diagnosis, and Therapeutic Advances. Int J Mol Sci. 2024 Sep 15;25(18):9966. doi: 10.3390/ijms25189966

6. Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, et al. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science. 1994 Jun 17;264(5166):1772-5. doi: 10.1126/science.8209258.

7. Leigh PN, Swash M, Iwasaki Y, Ludolph A, Meininger V, Miller RG, Mitsumoto H, Shaw P, Tashiro K, Van Den Berg L. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004 Jun;5(2):84-98. doi: 10.1080/14660820410020187.

8. Mead RJ, Shan N, Reiser HJ, Marshall F, Shaw PJ. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nat Rev Drug Discov. 2023 Mar;22(3):185-212. doi: 10.1038/s41573-022-00612-2

9. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, Mann D, Tsuchiya K, Yoshida M, Hashizume Y, Oda T. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Biochem Biophys Res Commun. 2006 Dec 22;351(3):602-11. doi: 10.1016/j.bbrc.2006.10.093.

10. Nijs M, Van Damme P. The genetics of amyotrophic lateral sclerosis. Curr Opin Neurol. 2024 Oct 1;37(5):560-569. doi: 10.1097/WCO.0000000000001294.

11. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci. 1994 Jul;124 Suppl:96-107. doi: 10.1016/0022-510x(94)90191-0.

12. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000 Dec;1(5):293-9. doi: 10.1080/146608200300079536.

13. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, Mills K, Mitsumoto H, Nodera H, Shefner J, Swash M. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008 Mar;119(3):497-503. doi: 10.1016/j.clinph.2007.09.143.

14. Shefner JM, Al-Chalabi A, Baker MR, Cui LY, de Carvalho M, Eisen A, Grosskreutz J, Hardiman O, Henderson R, Matamala JM, Mitsumoto H, Paulus W, Simon N, Swash M, Talbot K, Turner MR, Ugawa Y, van den Berg LH, Verdugo R, Vucic S, Kaji R, Burke D, Kiernan MC. A proposal for new diagnostic criteria for ALS. Clin Neurophysiol. 2020 Aug;131(8):1975-1978. doi: 10.1016/j.clinph.2020.04.005

15. van Eijk RPA, Westeneng HJ, Nikolakopoulos S, Verhagen IE, van Es MA, Eijkemans MJC, van den Berg LH. Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials. Neurology. 2019 Jan 28;92(5):e451-e460. doi: 10.1212/WNL.0000000000006855.

16. Young CA, Chaouch A, Mcdermott CJ, Al-Chalabi A, Chhetri SK, Talbot K, Malaspina A, Mills R, Tennant A. Improving the measurement properties of the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R): deriving a valid measurement total for the calculation of change. Amyotroph Lateral Scler Frontotemporal Degener. 2024 May;25(3-4):400-409. doi: 10.1080/21678421.2024.2322539.

17. Fournier CN, Bedlack R, Quinn C, Russell J, Beckwith D, Kaminski KH, Tyor W, Hertzberg V, James V, Polak M, Glass JD. Development and Validation of the Rasch-Built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS). JAMA Neurol. 2020 Apr 1;77(4):480-488. doi: 10.1001/jamaneurol.2019.4490.

18. Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS): Clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis - Scientific guideline | European Medicines Agency (EMA)

19. Strong MJ, Abrahams S, Goldstein LH, Woolley S, Mclaughlin P, Snowden J, Mioshi E, Roberts-South A, Benatar M, HortobáGyi T, Rosenfeld J, Silani V, Ince PG, Turner MR. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. Amyotroph Lateral Scler Frontotemporal Degener. 2017 May;18(3-4):153-174. doi: 10.1080/21678421.2016.1267768. Epub 2017 Jan 5. PMID: 28054827; PMCID: PMC7409990.