28 January 2016
EMA/CHMP/131550/2015
Committee for Human Medicinal Products (CHMP)

Overview of comments received on ' Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS)' (EMA/531686/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Cytokinetics
2	Biogen Idec
3	GSK
4	Hoffmann-la Roche Ltd
5	ENCALS (European Network for the Cure of ALS)
6	Cochrane neuromuscular disease group
7	Prof Philip van Damme, University Hospital Leuven*

* Comments were received before external consultation and partly implemented at that time point in the draft Guideline

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**4. General strategy for developing products for the treatment of ALS** 4.1 General strategy **Comment:** Cytokinetics notes the following statement, "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." We propose that treatments that can be demonstrated to produce measurable and clinically important improvements in patient function, while also likely to improve certain symptoms associated with skeletal muscle weakness, should be distinguished from treatments that improve symptoms (e.g., drooling or pseudo-bulbar affect) without associated improvements in overall patient function. Accordingly, we propose to add additional language to read as follows, "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, whether the treatment effect is expected to produce measurable and clinically important improvements in patients' functional status, or whether the treatment effect is expected to be purely symptomatic."	See specific comments below. **Not endorsed.**
1	4.2 Study objectives	**Not endorsed.** Non-specific symptomatic treatment is not

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	Comment: Consistent with the above point under 4.1, Cytokinetics proposes to add additional language to the third bullet and add a fourth bullet, as follows: The following study objectives could be considered: • Increased survival • Delay or stabilisation of disease progression • Clinically important improvement in patients' functional status, likely also in association with improvement of symptoms of ALS • Improvement of symptoms of ALS without improvements in patients' functional status	within the scope of this guideline. See also specific comments below.
1	5. Patients characteristics and selection of patients 5.1 Diagnostic criteria **Comment:** In section 5.1 regarding diagnostic criteria, it states that only ALS patients with "probable" or "definite" ALS according to the modified El Escorial (EE) criteria should be included in clinical trials. This can pose a major disadvantage of restricting clinical trials to patients with extensive clinical burden of disease and who may be too advanced to intervene upon their disease. Recent clinical trials evaluating disease modifying therapy aim to target specific neurodegenerative mechanisms earlier in the disease and as a result, have shortened the time from symptom onset (disease duration) for inclusion in these trials. In order to capture patients earlier in the disease, patients categorized as "possible ALS"	**Accepted.** See specific comments on text below.

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	by the modified EE criteria have been included, as in the recent multinational trial of dexpramipexole in ALS (Cudkowicz et al., 2013). This resulted in no errors in diagnosis in patients classified as having possible ALS. Although the modified EE criteria are specific, they lack sensitivity, particularly at the early stages of ALS when patients may benefit most from potential disease modifying therapy (Traynor et al., 2000). Amyotrophic lateral sclerosis (ALS) remains a clinical diagnosis without validated biomarkers. Additionally, a retrospective analysis of patients referred over a 6-month period to the electromyography laboratory for suspected motor neuron disease showed a higher agreement of the Awaji modifications than the Airlie House criteria with the clinical diagnosis of ALS (Chen et al., 2010)	
1	5.2 Inclusion and exclusion criteria **Comment:** Cytokinetics has no further comment on this topic.	
1	**Therapeutic Efficacy Measures** 6.1 Survival and time to failure analyses 6.2 Functional measures 6.3 Muscle strength measurements 6.4 Respiratory function measurements 6.5 Assessment of Health Related Quality of Life 6.6 Global measures **Comment:** Cytokinetics has no comment on this topic.	

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1	**8. Clinical Efficacy Studies** 8.1 Exploratory studies 8.2 Therapeutic confirmatory studies 8.2.1 Trials for disease modifying treatments **Comment:** Currently in section 8.2.1 regarding study design and choice of control groups in trials for disease modifying therapy, the text reads “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.” Cytokinetics believes that randomized, double-blind, placebo controlled studies of no more than 6 months durations are sufficient to establish the safety and efficacy of treatment that are aimed at decreasing symptoms or improving function in ALS. Assessment of safety and efficacy for potential therapies that can improve patient function (and muscle strength or fatigue) and should be amenable to evaluation in clinical trials of no more than 6 months, similar to what have been done for cholinesterase inhibitors for treatment of cognitive symptoms in Alzheimer’s Disease (Rogers et al., 1998), rasagiline mesylate for the treatment of early Parkinson disease (Parkinson Study Group, 2002), and tetrabenazine for the treatment of chorea in Huntington’s Disease (Huntington Study Group, 2006).	**Not accepted.** Recommendation for 6 months trials not included.

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1	8.2.2. Trials for symptomatic treatments **Comment:** As noted above under Section 8.2.2., Cytokinetics proposes that treatments that can be demonstrated to produce measurable and clinically important improvements in patient function, while also likely to improve certain symptoms associated with skeletal muscle weakness, should be distinguished from treatments that improve symptoms (e.g., drooling or pseudo-bulbar affect) without associated improvements in overall patient function. Accordingly, we propose the following changes: • The title of Section 8.2.2 should be changed to "Trials for treatments to improve patient function or to relieve symptoms of ALS" The first sentence in the sub-section, "Study duration" should be amended to read as follows, "Study duration for medicinal products with an effect to improve patient function or only to relieve symptoms without improvements in patient function may in principle be of shorter duration than for products with potential disease modifying effects.	**Partly accepted.** See specific comments below.
1	8.3 General methodological considerations **Comment:** Cytokinetics has no further comment on this topic.	
1	9. Studies in Special Populations **Comment:** Cytokinetics has no comment on this topic.	
1	10. Safety Evaluations **Comment:** Cytokinetics has no comment on this topic.	
3	Clinical trials in ALS and data they generate would be greatly enhanced by the adoption of an ALS disease staging system, particularly for the evaluation of treatments that are potentially	See specific comments below. Survival is important and data on this should be collected prior to approval. See modifications on the concept of co-

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	disease modifying. GSK encourages CHMP to embrace ongoing discussions to this end. We consider the revised El Escorial Criteria, even though internationally recognized, as being too blunt a tool for ALS clinical trials and advocate its replacement by an ALS disease staging system. Long-term disease progression endpoints are suboptimal for efficiently and effectively exploring the dose-response relationship of an investigational medicine in this rare and life-threatening disease. A more efficient approach would be to explore relationships between compound exposure, target engagement, pharmacodynamics, biomarker and/or surrogate marker data to better describe the dose- / exposure-response curve, and using modelling and simulation as necessary. The use of placebo control in clinical studies in ALS should be reduced when scientifically and ethically appropriate. To do this, it is important to promote the generation, publication and sharing of high quality ALS natural history data including the data from placebo arms in ALS clinical trials. Primary endpoints in recent efficacy trials have used a combined measure of function and survival. There is a need to explore and then validate other outcome measures. Study assessments in ALS clinical trials must balance the scientific needs of the investigation with the burden of the assessments on the trial patient. GSK supports the CHMP's aim of providing formal guidance on the development pathways for demonstrating the benefit-risk profile of a medicine for the treatment of ALS. However, we are concerned that the guideline has too strong a focus on survival as a primary	primary endpoints in sections 8.2. and 6.1./ 6.2.

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	(registration) endpoint. This could delay the access of new authorized treatments for ALS because of the difficulty of conducting long mortality trials in a rare disease. It should be implicit that the important question of confirmation of a beneficial effect on survival can be answered from data obtained from post-authorization studies or registries. This would be consistent with approaches such as conditional marketing authorization and the more recent concept of medicines adaptive pathways to patients (MAPP). In this way, the guidance should have regard to an evolving benefit-risk of medicines for treating ALS, not only through the clinical development but also once on the market.	
4	In Line 50 ALS is described as 'fatal', and the Introduction section (Lines 99 - 100) goes on to describe treatment as mainly palliative and supportive measures'. This is consistent with the general understanding of the severity and life-threatening nature of the disease.	No change required. See Executive summary and 1. Introduction
5	In general the membership of ENCALS welcomes the document entitled 'Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS)'.	No change required
5	Therapeutic Efficacy Measurement **Functional outcome** Should consider change in declining cognitive status as a possible secondary end point, once scales have been validated. Delayed start design trials could be considered to differentiate	**Accepted.** In section 6.7 Cognitive functioning was included as additional endpoint. **Accepted.** See section 8.2.1. Efficacy endpoints and

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	protective role from symptomatic effect.	methodological considerations: “Alternative study designs such as delayed start design trials could be considered to differentiate a disease modifying from a symptomatic effect.”
6	Cochrane Neuromuscular Disease Group, which publishes Cochrane systematic reviews of interventions in amyotrophic lateral sclerosis and other neuromuscular conditions: We have no formal comment or representation to make on the consultation on draft guidelines on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis. However, we have provided the attached list of Cochrane systematic reviews of medicinal interventions in ALS, which may be of value. Full text versions of the reviews are available on *The Cochrane Library* http://www.thecochranelibrary.com/view/0/index.html.	10 Cochrane reviews on treatment of ALS were provided which are of interest but since this is not a treatment guideline they have no direct impact on the content of the Guideline.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 74-82	**7**	Comments: Not entirely up to date, some FUS mutations present at early age, and other mutations in FUS give more classical ALS.	**Agreed.** Section is modified and respective lines deleted. All is said by "Although FALS is clinically and genetically heterogeneous the clinical presentation of FALS and SALS ~~can be~~ is very similar."
Lines 87-100	**5**	Comments: It is now recognized that cognitive and behavioural impairment comprise an important component of the clinical phenotype, affecting up to 50% of patients, with up to 13% exhibiting features of fronto-temporal dementia: (*Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, Lynch C, Pender N, Hardiman O. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry. 2012 Jan;83(1):102-8.).* This should be included as part of the phenotype, particular as executive dysfunction is an important predictor of survival. *Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B, O'Brien C, PhukanJ, Lynch C, Pender N, Hardiman O. Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology. 2013 Apr 23;80(17):1590-7. .* *Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N, Hardiman O. Executive dysfunction is a*	**Partly accepted.** "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 co-morbid FTD (see also section 6.7) (Strong 2009, Phukan 2012)." "In patients without dementia, executive dysfunction is an important negative prognostic indicator (Elamin et al. 2011, 2013)." See also comment on section 8.3 below.

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		negative prognostic indicator in patients with ALS without dementia. Neurology. 2011 Apr 5;76(14):1263-9.	
99	**5**	Comments: Treatment is palliative but should include riluzole, for where there is an evidence based supporting efficacy.	**Accepted. Revised wording included in the introduction:** **"**Riluzole is the only approved medication for modifying disease progression in ALS and apart from that treatment is mainly palliative (Miller et al 2009, EFNS guideline 2012)."
146-148	**1**	Comments: In section 4.1 regarding general strategy, it states that "[t]he 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." We propose that treatments that can be demonstrated to produce measurable and clinically important improvements in patient function, while also likely to improve certain symptoms associated with skeletal muscle weakness, should be distinguished from treatments that improve symptoms (e.g., drooling or pseudo-bulbar affect) without associated improvements in overall patient function. Proposed change (if any): We propose to add additional language to read as follows: "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	**Not accepted. See below.**

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		activity whether the treatment effect is expected to produce measurable and clinically important improvement in patient´s functional status, or whether the treatment effect is expected to be purely symptomatic."	
148	**2**	Comment: Given the high unmet need, consideration should be given to allow for alternative study design options that do not require a placebo arm (e.g., double dummy design). Proposed change (if any): Studies should preferably be randomized, double-blind and placebo-controlled (see section 8). However, given the high unmet need, consideration will be given to allow for alternative study design options that do not require a placebo arm (e.g., double dummy design).	**Not accepted.** Also add-on double dummy designs are placebo controlled studies. No need for modification since this is explained in section 8. See also below comment on lines 303-306.
Lines 154-159	**1**	**Comment:** In section 4.2 regarding study objectives, it states that "[t]he 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	**Partly accepted.** "Improvement of symptoms of ALS, e.g. muscle strength and related function." **Non-specific symptomatic treatment is not within the scope of this guideline. See also general comments above.**

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		Proposed change (if any): We propose to add additional language to read as follows: The following study objectives could be considered: • Increased survival • Delay or stabilisation of disease progression • Clinically important improvement in patients' functional status, likely also in association with improvement of symptoms of ALS • Improvement of symptoms of ALS without improvements in patients' functional status	
158	**4**	Comment: It would be helpful to have some guidance on whether a slope analysis of a functional endpoint, such as ALSFRS-R, is sufficient for demonstrating "delay or stabilisation of disease progression", or if a time-to-event analysis is required.	**Not accepted in this section** since it refers to Primary endpoints and methodological considerations in section 8.2.
166	**5**	The presence of the C9orf72 hexanucleotide repeat expansion is an important predictor of phenotype, pathology, imaging and progression, and this should be recognized. *Cooper-Knock J, Hewitt C, Highley JR, Brockington A, Milano A, Man S,Martindale J, Hartley J, Walsh T, Gelsthorpe C, Baxter L, Forster G, Fox M, Bury J, Mok*	**Not accepted.** Not too many stratification factors should be mentioned. See below comment to ll 175-176. "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)."

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		K, McDermott CJ, Traynor BJ, Kirby J, Wharton SB, Ince PG, Hardy J, ShawPJ. Clinico-pathological features in amyotrophic lateral sclerosis with expansions in C9ORF72. Brain. 2012 Mar;135:751-64) *Bede P, Bokde AL, Byrne S, Elamin M, McLaughlin RL, Kenna K, Fagan AJ, Pender N, Bradley DG, Hardiman O. Multiparametric MRI study of ALS stratified for the C9orf72 genotype. Neurology. 2013 Jul 23;81(4):361-9.* *Byrne S, Elamin M, Bede P, Shatunov A, Walsh C, Corr B, Heverin M, Jordan N, Kenna K, Lynch C, McLaughlin RL, Iyer PM, O'Brien C, Phukan J, Wynne B, Bokde AL, Bradley DG, Pender N, Al-Chalabi A, Hardiman O. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neurol. 2012 Mar;11(3):232-40.*	and "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)." is mentioned in the Introduction instead.
169-176	**5**	Cognitive /behavioural impairment may also pre-date motor deficits and this should be recognized.	**No change required.** "Due to the variability in clinical findings…" See also section 1 where cognitive impairment is mentioned as an important component of the clinical phenotype.
175-176	**2**	**Comment:** Given the limited knowledge of ALS, the guideline should remain open to other possibilities for stratification. There are more than two prognostic factors so it would be helpful to clarify that these two	Accepted. "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)."

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		prognostic factors are examples and not the entire list. **Proposed change (if any):** Study participants should be stratified according to known prognostic factors, ~~i.e.~~ e.g. bulbar signs and time from first symptom to diagnosis (Beghi 2011) and concomitant use of riluzole.	
175	**5**	Stratification parameters should include C9orf92 status and cognitive status.	Not accepted. See above.
179	**5**	"Diagnosis is mainly clinical (please add: AND BY EXLUSION OF OTHER DISORDERS) and should be based on the revised El Escorial Criteria (EEC)'	**Not accepted.** By exclusion of other disorders is also clinical and is mentioned in the revised El Escorial Criteria.
183	**7**	We performed validation of the newer criteria (Schrooten et al., Annals of neurology 2011, PMID: 21437935)	Reference included already before external consultation. The Awaji criteria are not fully validated yet.
185-186	**1**	**Comment:** The text under section 5.1, regarding diagnostic criteria, states, "Only patients with definite or probable ALS according to the modified EE criteria should be included in clinical trials". Recent trials for disease modifying therapy have required shorter disease duration and would require inclusion of patients that are categorized as "possible ALS" according to the modified EE criteria. It is likely that disease modifying therapy would have the greatest potential to have an effect when started	Accepted with slightly modified wording: "Patients with a diagnosis of definite, probable or possible ALS are eligible to be included in clinical trials."

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		earlier in the disease. Additionally, symptomatic treatments target specific symptoms of the disease and inclusion of “possible” ALS according to the modified EE criteria would be appropriate. We would propose the following, “Patients with definite, probable or possible ALS according to the modified EE criteria should be included in the clinical trials”. **Proposed change (if any):** ~~Only~~ P~~p~~atients with definite, ~~or~~ probable or possible ALS according to the modified EE criteria should be included in the clinical trials.	
185-186	**2**	**Comment:** Patients with definite and probable ALS have more diffuse and often later and more progressive disease. Consideration should be given to inclusion of patients with a diagnosis of possible ALS (Traynor 2000). **Proposed change (if any):** ‘~~Only patients with definite or probable ALS according to the modified EE criteria should be included in clinical trials.~~ Patients with a diagnosis of definite, probable or possible ALS may be included in clinical trials. The use of the modified EEC…’	See above

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185-186	**4**	Comment: It would be helpful to be provided with a rationale as to why it is recommended to only include patients with definite or probably ALS into clinical trials. Proposed change (if any):	See above. Patients with possible ALs are also included.
186	**5**	Definite, Probable, Laboratory Supported Probable and Possible ALS should be included in clinical trials.	See above
185-186	**3**	**Comment:** We consider the guidance as being too conservative regarding diagnosis. There is typically a delay of up to one year between the disease onset and the diagnosis. A definite diagnosis of ALS is likely to be established in some patients even further into the course of the disease which, in some cases, could be too late for showing a meaningful benefit. Many patients in the possible ALS category can be accurately diagnosed by suitably experienced physicians. Preventing possible ALS patients from entering clinical trials, of whom many would have ALS in its early stages, will have a negative impact on finding new treatments that can have the greatest beneficial effect at the early stages of the disease. Once a more sensitive diagnosis tool is internationally agreed (for example an ALS disease staging system), its use should be recommended in a revision to the guideline. **Proposed change:** ~~Only~~ Patients with definite, ~~or~~ probable or possible ALS according to the modified EE criteria should be	Partly accepted. See above. Other neurological conditions should always be excluded not only in possible ALS.

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		included in clinical trials. Inclusion of possible ALS patients may require additional justification and assurance of an accurate diagnosis, for example, by exclusion of other neurological conditions that could mimic ALS.	
185-186	**7**	Many trials allow patients with possible ALS. In experienced centers they virtually always turn out to have ALS. Early recruitment of patients is important, not allowing patients with possible ALS hampers the inclusion of patients with early disease.	See above
192	**3**	**Comment:** A significant proportion of ALS patients have some degree of cognitive impairment. The reason for the guideline requiring exclusion of subjects with significant cognitive and/or behavioural impairment, clinical dementia or psychiatric illness should therefore be explained. The effect of mental status on trial outcomes is usefully discussed in lines 370-374. Similar discussion on cognitive impairment, dementia and psychosis would be helpful.	**Accepted.** Exclusion criterion modified to patients with severe active psychiatric illness because of ethical and feasibility reasons. The effect of cognitive function on efficacy outcome is now mentioned in section 8.3. and section 1.
192	**5**	As cognitive impairment is an important feature of ALS, the ENCALS group is of the opinion that this should be deleted as an exclusion criterion for trials.	Accepted. Exclusion criterion was modified. - Subjects with ~~significant cognitive impairment, clinical dementia or~~ severe active psychiatric illness See line 208 However, after patients lose their ability to communicate effectively, the reliable evaluation of cognition is limited, leaving open the question of the capacity to make sound

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			treatment decisions or apply appropriate judgment.
Section 6, **No line indicated**	**5**	Other outcome measures could be the recently developed and reported 'staging' scales: Chiò A, Hammond ER, Mora G, Bonito V, Filippini G. Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. Neurol Neurosurg Psychiatry. 2013 Dec 13. Balendra R, Jones A, Jivraj N, Steen IN, Young CA, Shaw PJ, Turner MR, Leigh PN, Al-Chalabi A; UK-MND LiCALS Study Group, Mito Target ALS Study Group. Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J Neurol Neurosurg Psychiatry. 2014 Jan 24.	**Accepted.** Additional bullet point included under 6.7. ***"6.7. Additional endpoints*** **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) should 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)."
204	**3**	**Comment:** As stated in line 154, *the primary goal of ALS treatment is the prevention or delay of disease progression*. Lines 154 and 204 therefore have an apparent contradiction. Survival as a primary endpoint should not be given implied precedence over functional endpoints that are sensitive and informative in evaluating the prevention or delay in disease	**Accepted** with reference to section 8.2 where further explanation is given. "If it is not used as primary endpoint it should at least be secondary (see section 8.2)."

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		progression. Furthermore, a focus on survival as a primary (registration) endpoint could delay the access of new authorized treatments for ALS because of the difficulty of conducting lengthy mortality trials in a rare disease. **Proposed change:** Survival time should normally be an ~~primary~~ endpoint of ALS trials aiming at disease modification.	
219-220	**2**	**Comment:** The measurement of minimally important treatment effect size is not clear. To avoid arbitrary a priori definitions, we suggest the text allow for use of pre-specified approaches (e.g., cumulative response curves). **Proposed change (if any):** "… should be defined a priori. Anchor-based methods and cumulative response curves may aid in interpreting minimally important differences between treatment and comparator arms."	**Not accepted.** There are more options to justify a clinically meaningful outcome. The minimum treatment effect size that could be considered clinically meaningful as outcome in clinical trials should be defined and justified a priori. See next comment below. The sentence was finally changed to "A response criterion effect size that could be considered clinically meaningful as outcome in clinical trials should be defined and justified a priori." and moved to section 8.2.1. Efficacy endpoints and methodological considerations
222	**5**	The Norris scale (Norris 1974), the Appel Scale 222 (Appel 1987) and the ALS Severity Scale (ALSSS; Hillel 1989) should not be recommended to include in trials according to ENCALS	**Partly accepted.** It should be acknowledged that these scales were previously used to assess function but the ALSFR-R is mentioned as the preferred scale.
224-225	**2**	**Comment:**	**Accepted with slightly modified wording.**

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		The ALSFRS-R has recognized limitations (Franchignoni et al., 2013). Measurement of functioning in ALS may be improved with new outcomes measures or with modifications to current measures. We recommend that the guidance recognize this and allow for the use of new primary and/or secondary endpoints in future trials. **Proposed change (if any):** "…least be secondary. If a newly developed and validated measure of function is used as a primary or secondary endpoint, a rationale for its use should be made."	"If a newly developed and validated measure of function is used as endpoint, a rationale for its use should be made (Franchignoni 2013)."
224-225	**3**	**Comment:** To be consistent with the statement in line 154 - *the primary goal of ALS treatment is the prevention or delay of disease progression* – functional endpoints, preferably ALSFRS-R, should normally be primary, co-primary or included as part of a combined assessment of function and survival as primary. **Proposed change:** …however the ALSFRS-R should be the preferred scale. I~~f it is not used as primary endpoint i~~t should normally ~~at least~~ be ~~secondary~~ primary, co-primary or included as part of a combined assessment of function and survival as primary for ALS trials aiming at disease modification.	**Not accepted in this section.** Revisions are included in section 8. "/…/ however the ALSFRS-R ~~should be~~ is the preferred scale."

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253	**2**	**Comment:** The guideline should be revised to mention the EQ-5D or preference-based measures such as the Health Utilities Index (HUI). **Proposed change (if any)**: "Both generic (e.g. SF-36, EQ-5D, the Health Utilities Index (HUI), Sickness Impact Profile [SIP])(Bergner 1981) and specific…"	**Accepted.**
258-259	**2**	**Comment:** CGI scales are useful in anchor-based methods of clinical meaningful change and minimally important differences in treatment effect. **Proposed change (if any):** "… as therapeutic effects. In addition, the CGI may be useful in anchor-based assessments of clinically meaningful change."	**Accepted.**
267-275	**3**	**Comment:** Given that >90% of ALS comprises patients with no family history or no mutation identified, recommendation of continuous use of relatively well characterized (SOD-1) or newly developed/developing genetic models (TDP-43, C9ORF72 etc.) for drug screening is unclear, especially when their clinical predictive value (positive or negative) is unknown or yet to be established. We would appreciate more	**No change required.** No further recommendation can be given (see also Ludolph 2010: *Guidelines for preclinical animal research in ALS/MND: A consensus meeting. Amyotroph Lateral Scler. 2010;11(1-2):38-45.)* "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

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		discussion on the importance of ***criteria*** in selecting the appropriate model, e.g., on the choice of acute motor neuron injury models versus transgenic models.	mutations in TDP-43, FUS/TLS, C90RF72, EPhA4 etc.; Bendotti 2004; 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)." This wording was approved by SWP. See general comments above.
267-270	**5**	Should reference : *Bendotti C, Carri MT. Lessons from models of SOD1-linked familial ALS. Trends Mol Med. 10(8):393-400, 2004.*	**Accepted.** The reference was included in the list.
275	**5**	Reference; *Guidelines for preclinical animal research in ALS/MND: A consensus meeting.Ludolph AC, Bendotti C, Blaugrund E, Chio A, Greensmith L, Loeffler JP, Mead R, Niessen HG, Petri S, Pradat PF, Robberecht W, Ruegg M, Schwalenstöcker B, Stiller D, van den Berg L, Vieira F, von Horsten S. Amyotroph Lateral Scler. 2010;11(1-2):38-45.*	The reference was included in the list.
276	**3**	**Comment:** It would be helpful to have more guidance on human in vitro models, e.g., on iPS cells.	References are included in the list (Dimos 2008, Coatti 2015) but premature to give further guidance.
283-289	**3**	**Comment:** The size and duration of a "classic" parallel arm, fixed dose study employing an efficacy endpoint makes this an unattractive approach in this rare, chronic and life-threatening disease.	**Accepted with further modification.** See section 8.1. ***/ … /*** "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." ~~but in any event robust data allowing comparison of at least three doses are~~

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		Proposed change: 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. In certain circumstances it may be appropriate to conduct phase I studies in ALS patient, such as when the target mechanism is not expressed in healthy subjects. 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. The use of pharmacokinetic / pharmacodynamic data to assist in 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. 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, but in any event robust data ~~allowing comparison~~ of at least three different doses are necessary to establish a dose response relationship.	~~necessary to establish a dose response relationship.~~
293-295	**3**	**Comment:** The inclusion of the Lacomblez and Pascuzzi references implies there is a debate about the utility of functional measures in exploratory clinical trials in ALS, when there is overwhelming evidence that functional evaluations such as ALSFRS-R provide meaningful clinical data. . ALSFRS-R is a validated clinical outcome	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		measure in ALS which is widely accepted as a gold standard and is being extensively used in clinical trials. This is further supported by Gordon [ALS and Other Motor Neurone Disorders 2004; 5(suppl 1):90-3], de Carvalho [Amyotrophic Lateral Sclerosis 2005; 6:202-212] and Leigh [ALS and Other Motor Neurone Disorders 2004; 5:84-98] amongst many others. Moreover, Cedarbaum [Journal of Neurological Sciences 1999; 169:13-21] presents data correlating baseline ALSFRS-R score with 9 months survival. **Proposed change:** ~~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).~~	
303-306	**2**	**Comment:** Given the high unmet need, consideration should be given to allow for alternative study design options that do not require a placebo arm (e.g., double dummy design). **Proposed change (if any):** "To assess the effects of medicinal products for treatment of patients with ALS parallel, double blind, randomised placebo controlled trials are ~~necessary~~ preferred. However, given the high unmet need, consideration will be given to allow for alternative study design options that do not require a placebo arm	**Not accepted.** This comment is not well understood: Double dummy contains a placebo arm in add-on. See also above comments on line 148.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(e.g., double dummy design). 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. ”	
303-306	**3**	**Comment:** The use of placebo control in clinical studies should be reduced when scientifically and ethically appropriate. This approach will allow fewer patients to be randomized to placebo when the potential benefits of a medicine become better understood. To assist this intention, it is important to promote the generation, publication and sharing of high quality ALS natural history data including the data from placebo arms in ALS clinical trials. GSK encourages the sharing of this data in the EU and internationally, for instance by expanding an open-access database. **Proposed change:** To assess the effects of medicinal products for treatment of patients with ALS parallel, double blind, randomised placebo controlled trials are necessary. Relevant historical control group data on survival and other key outcome measures may be used in order to reduce the number of placebo subjects recruited into a clinical trial. ~~instead of a placebo control are not acceptable~~ However, ~~due to changes~~ it will be necessary to ensure similarities in diagnostic criteria, variability of patient populations and ~~evolving changes in~~ standard of care ~~of these patients~~ between	**Not accepted.** Historical controls not acceptable due to the reasons mentioned. See below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the historical and concurrent patient groups.	
318-322	**1**	**Comment:** Currently in section 8.2.1 regarding study design and choice of control groups in trials for disease modifying therapy, the text reads “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.” Cytokinetics believes the best approach to the clinical evaluation of a potential new dug for the treatment of ALS patients is to compare the potential new drug to placebo over a background of standard therapy, including riluzole. However, it might not be feasible to have “sufficient” numbers in both riluzole and non-riluzole categories from our experience. Although riluzole is standard of care, its use in ALS patients is a variable in different geographical regions for a variety of reasons. **Proposed change (if any):** We would like to propose the following, “In this case recruitment should be stratified by riluzole use and should aim to achieve sufficient numbers in both categories to achieve ~~sufficient numbers in both categories to achieve~~	**Not accepted.** Last part of the sentence is deleted since this is difficult to handle if the overall results of the trial are negative.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~sufficient~~ reasonable statistical power for showing consistent results in both categories; ie., there should be sufficient numbers in each stratum to exclude a clinically important interaction effect between the two strata but not necessarily sufficient numbers to demonstrate a statistically significant treatment effect within each stratum."	
321-322	**2**	**Comment:** In general, subgroup analyses are not powered. This should be clarified in the guidance by stating that subgroup analyses are exploratory in nature. **Proposed change (if any):** "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~~ allow for the conduct of meaningful exploratory subgroup analyses . "	**Partly accepted.** See above.
326-327	**3**	**Comment:** The requirement for two (co-)primary endpoints, one measuring functional disability, the other survival should be more flexibly stated. As commented above, a requirement for survival as a (co-)primary endpoint in a confirmatory trial could delay the access of new authorized treatments for ALS because of the difficulty of conducting lengthy mortality trials in a rare disease. The guidance should allow for demonstration of a significant benefit based on delayed disability or	**Partly accepted.** See alternative wording as indicated above: "In general ~~primary~~ endpoints from the domains of disability and~~/or~~r survival should be prespecified to estimate slowing of disease progression and~~/or~~ increased survival. ~~Important~~ As primary efficacy variable~~s~~ in ALS trials 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) ~~and~~ or function (ALSFRS-R) (see section 6) or

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		survival, or both. **Proposed change:** In general, ~~two~~ primary endpoints from the domains of disability and/or survival should be prespecified to estimate slowing of disease progression and/or increased survival.	both can be used. 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."
325-333	**3**	**Comment:** Further guidance is requested in this section on statistical analysis methods appropriate for survival and functional data in ALS, including handling missing data and the use of composite endpoints, for example combined assessment of function and survival (CAFS), as discussed Berry 2013 [Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration 2013; 14(3):162-168.	**Partly accepted.** The overall results should not be driven by a change in one or the other or both. Specific recommendations on statistical analysis methods are not included. This should be subject to scientific advice
326-328	**2**	**Comment:** The use of time to death as a primary endpoint would require a large trial which would be extremely challenging to execute and perhaps unfeasible in a rare disease. While the domains of disability and survival are important and create the opportunity for a novel endpoint that combines both domains, these should not be the requirement for a primary endpoint so long as both parameters are being measured through the secondary endpoints. Also analyzing ALSFRS-R in the presence of death is challenging as standard missing data techniques aren't applicable. Consideration should be given to the use of combined endpoints such	**Partly accepted.** "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." See below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		as the Combined Assessment of Function and Survival (CAFS) which allows for the simultaneous analysis of survival and ALSFRS-R change. CAFS is based on a joint rank which is derived from patients ' clinical outcomes based on survival time and change in the ALSFRS-R score (Berry 2013, Finkelstein 1999). It has been accepted as a primary endpoint for Phase III studies Cudkowicz 2013). **Proposed change (if any):** "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). Use of, for example, the Combined Assessment of Function and Survival (CAFS) endpoint which allows for the simultaneous analysis of survival and ALSFRS-R change in a combined end point, could be considered. Due to…	
331-332	**2**	**Comment:** The guidance should be expanded to consider disease progression models and group sequential designs. **Proposed change (if any):** "…tracheostomy). Where possible, disease progression models should be	**Partly accepted.** Staging of disease progression is mentioned in Section 6.7. Additional endpoints. **Not accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered for designing a population enrichment strategy to help minimize the heterogeneity of patients enrolled in new trials (Gomeni 2013). Where applicable, group sequential designs should be considered to facilitate futility analyses for Phase 2 or Phase 3 studies. If alternative strategies…"	
334	**1**	**Comment:** We propose the title of Section 8.2.2 should be changed. **Proposed change (if any):** **8.2.2. Trials for symptomatic treatments to improve patient function or relieve symptoms of ALS**	**Partly accepted.** **8.2.2. Trials for symptomatic treatments and related function**
352-354	**1**	**Comment:** In Section, 8.2.2, the first sentence in the sub-section, "Study duration" should be amended to read as follows: **Proposed change (if any):**	**Not accepted.** Non-specific symptomatic treatments are without the scope of this guideline. See also above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Study duration Study duration for medicinal products with an effect to improve patient ~~only on symptomatic improvement (e.g. muscle strength and related~~ function or only to relieve symptoms without improvements in patient function~~)~~ may in principle be of shorter duration than for products with potential disease modifying effects.	
368-369	**3**	ALS patients can find numerous assessments very taxing. The demands of the clinical trial design should not be overtaxing for the patient. **Proposed change:** 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. Study assessments in ALS clinical trials must balance the scientific needs of the investigation with the burden of the assessments on the trial patient.	**Not accepted since generally valid.**
370-374	**2**	**Comment:** Cognitive decline is one of the most powerful predictors of outcome in ALS and should be considered in the guidance. **Proposed change (if any):**	**Accepted** since it is acknowledged that cognitive and behavioural impairment comprises an important component of the clinical phenotype not only in patients with co-morbid FTD (Phukan 2012). See also section 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~Mental state may be a possible confounding factor as psychological~~ 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 ~~mood~~ evaluation of mood and cognitive function in clinical trials and to evaluate the impact of these on efficacy outcome.	
375	**5**	The evidence does not support the statement that "ALS is rare in those over the age of 70". The mean age of ALS is increasing. This should be adjusted to at least 75. *Pupillo E, Messina P, Logroscino G, Beghi E; the SLALOM Group. Long-termsurvival of amyotrophic lateral sclerosis. A population-based study. Ann Neurol. 2014 Jan 2. doi: 10.1002/ana.24096. [Epub ahead of print] PubMed PMID: 24382602)* and mean age of onset is proportionate to the life expectancy of the population. (*Byrne S, Jordan I, Elamin M, Hardiman O. Age at onset of amyotrophic lateral sclerosis is proportional to life expectancy. Amyotroph Lateral Scler Frontotemporal Degener. 2013 Dec;14(7-8):604-7.*	**Accepted.** See below.
386	**4**	**Comment:** In the section dealing with Safety Evaluations, line 386	**Not accepted. No change required** since it is explicitly stated in ICH E1: In some cases, a smaller number of patients

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		references ICH E1 Note for guidance on population exposure, indicating that this guidance applies. The referenced guidance is specifically for drugs intended for long term treatment of non-life threatening diseases. If it is truly the intention that the ICH E1 guidance is to be followed for ALS treatments, which may be considered a high bar, especially for an orphan indication, then it would be helpful for this to be position to be justified.	may be acceptable, for example where the intended treatment population is small.
399-427	**2**	**Comment:** Consideration should be given to citing a reference for the table.	**Accepted.** Table is taken from Wijesekera et al 2009 according to Brooks et al 2000. Reference included in the list of References.
455	**2**	**Comment:** Consideration should be given to citing a reference for the table.	**Accepted.** Cedarbaum 1999
593-594	**2**	**Comment:** Suggest deleting this reference as it is not cited in the draft guideline. **Proposed change (if any):** ~~67. Schoenfeld DA et al. Design of phase II ALS clinical trials. Amyotrophic Lateral Sclerosis 9, 16-23 593 (2008)~~	**Accepted.** The section on exploratory trials was modified substantially. Reference is deleted.
References	**2**	**Comment:** Consideration should be given to adding the following references to the guideline. These are cited within this	**Accepted.** All references are included in the list.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		response. Proposed change (if any): “Berry et al. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials, Amyotroph Lateral Scler Frontotemporal Degener, 14, 162–168 (2013) Cudkowicz et al. Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial, The Lancet Neurology 12, 1059–1067 (2013) Finkelstein et al. Combining mortality and longitudinal measures in clinical trials, Stat Med 18, 1341-1354 (1999) Franchignoni et al. Evidence of multidimensionality in the ALSFRS-R scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry, Epub ahead of print (2013) Gomeni et al. Amyotrophic lateral sclerosis disease progression model, Amyotroph Lateral Scler , Early Online (2013) ”	