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Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial

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Summary

Background In a phase 2 study, dexpramipexole (25–150 mg twice daily) was well tolerated for up to 9 months and showed a significant benefit at the high dose in a combined assessment of function and mortality in patients with amyotrophic lateral sclerosis. We aimed to assess efficacy and safety of dexpramipexole in a phase 3 trial of patients with familial or sporadic disease.

Methods In our randomised, double-blind, placebo-controlled phase 3 trial (EMPOWER), we enrolled participants aged 18–80 years (with first amyotrophic lateral sclerosis symptom onset 24 months or less before baseline) at 81 academic medical centres in 11 countries. We randomly allocated eligible participants (1:1) with a centralised voice–interactive online system to twice-daily dexpramipexole 150 mg or matched placebo for 12–18 months, stratified by trial site, area of disease onset (bulbar *vs* other areas), and previous use of riluzole. The primary endpoint was the combined assessment of function and survival (CAFS) score, based on changes in amyotrophic lateral sclerosis functional rating scale–revised (ALSFRS-R) total scores and time to death up to 12 months. We assessed the primary endpoint in all participants who received at least one dose and had at least one post-dose ALSFRS-R measurement or died. We monitored adverse events in all participants. This study is registered with ClinicalTrials.gov, number NCT01281189.

Findings Between March 28, 2011, and Sept 30, 2011, we enrolled 943 participants (474 randomly allocated dexpramipexole, 468 randomly allocated placebo, and one withdrew). Least-square mean CAFS scores at 12 months did not differ between participants in the dexpramipexole group (score 441·76, 95% CI 415·43–468·08) and those in the placebo group (438·84, 412·81–464·88; p=0·86). At 12 months, we noted no differences in mean change from baseline in ALSFRS-R total score (–13·34 in the dexpramipexole group *vs* –13·42 in the placebo group; p=0·90) or time to death (74 [16%] *vs* 79 [17%]; hazard ratio 1·03 [0·75–1·43]; p=0·84). 37 (8%) participants in the dexpramipexole group developed neutropenia compared with eight (2%) participants in the placebo group, and incidence of other adverse events was similar between groups.

Interpretation Dexpramipexole was generally well tolerated but did not differ from placebo on any prespecified efficacy endpoint measurement. Our trial can inform the design of future clinical research strategies in amyotrophic lateral sclerosis.

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Introduction

Amyotrophic lateral sclerosis is a rapidly progressive disease that leads to debilitating upper and lower motor neuron dysfunction and death.[1,2] No cure exists for the disease at present. Only one approved therapy, riluzole, provides a modest effect on survival but no proven effect on muscle strength.[3–8]

Although progress has been made in understanding the complex pathophysiology of amyotrophic lateral sclerosis, no unifying model of disease pathogenesis exists. Therefore, identification of therapeutic targets is a substantial challenge. Mitochondria are key energy producers for neurons and are implicated in several neurodegenerative diseases, including amyotrophic lateral sclerosis; thus, drugs that target mitochondria might be useful for treatment.[9–14]

Dexpramipexole is thought to enhance mitochondrial function, is active in in-vitro assays of neuroprotection, and leads to increased rates of survival and retention of motor function in in-vivo models of amyotrophic lateral sclerosis.[15–17] Dexpramipexole was assessed in a two-part phase 2 study in amyotrophic lateral sclerosis.[18] In part 1 of the study (which provided participants 12 weeks of treatment), non-significant dose-dependent trends were noted toward a decrease in the slope of decline in amyotrophic lateral sclerosis functional rating scale–revised (ALSFRS-R) total score.[18] In part 2 of the study (which provided participants 24 weeks of treatment at two doses, compared with three doses in part 1), a significant difference was reported (p=0·046) in a prespecified sensitivity analysis comparing a twice-daily regimen of dexpramipexole 150 mg and 25 mg using the combined assessment of function and survival (CAFS;[18,19] a joint-rank test based on mortality and change from baseline in ALSFRS-R total score).[20] This study met the primary endpoint, which was safety, and dexpramipexole was generally well tolerated. The results from preclinical studies and favourable phase 2 results provided the rationale for further assessment of dexpramipexole in amyotrophic lateral sclerosis.

We aimed to assess efficacy and safety of twice-daily oral dexpramipexole 150 mg in participants with amyotrophic lateral sclerosis, with a null hypothesis that dexpramipexole was no better than placebo on the primary endpoint, the CAFS.

Methods

Study design and participants

In our double-blind, randomised, phase 3 study (EMPOWER), we enrolled adults aged 18–80 years with a diagnosis of possible, laboratory-supported probable, probable, or definite amyotrophic lateral sclerosis (familial or sporadic) in accordance with the revised El Escorial criteria.[21] Participants were enrolled at 81 academic medical centres in Australia, Belgium, Canada, France, Germany, Ireland, the Netherlands, Spain, Sweden, the UK, and the USA. Eligible participants had onset of first amyotrophic lateral sclerosis symptoms 24 months or less before baseline and an upright slow vital capacity of at least 65% of the predicted value for age, height, and sex at screening. Participants had to be able to swallow oral drugs on day 1.

See Online for appendix

We excluded participants meeting the following criteria: presence of significant cognitive impairment, clinical dementia, or psychiatric illness; other neurodegenerative disease (eg, Parkinson's disease or Alzheimer's disease); clinically significant history of unstable or severe cardiac, oncological, hepatic, or renal disease or other medically significant illness; pre-existing pulmonary disorder not attributed to amyotrophic lateral sclerosis; abnormal neutrophil count (defined as $<1 \cdot 96 \times 10^3$ cells per μL) at screening or a documented history of neutropenia; aspartate aminotransferase or alanine aminotransferase concentrations more than 3·0 times the upper limit of normal; creatinine clearance 50 mL/min or less; exposure to any other experimental drug (off-label use or investigational) up to 30 days before day 1; previous exposure to dexpramipexole; and present use of pramipexole or other dopamine agonists.

All participants provided written informed consent for the study and institutional review board approvals were received at all sites before enrolment. An independent data monitoring committee monitored safety throughout the study.

Randomisation and masking

We randomly allocated participants in a 1:1 ratio to receive twice-daily oral dexpramipexole (as dexpramipexole dihydrochloride) 150 mg or placebo (tablets matched in size, colour, presentation, and taste; provided by Biogen Idec) for up to 18 months or until the last participant completed 12 months, whichever came first. Randomisation was stratified by trial site, area of amyotrophic lateral sclerosis onset (bulbar *vs* other areas [limb, cervical, thoracic, or lumbar]), and use of riluzole (yes *vs* no). Randomisation was done with a centralised voice–interactive online response system, which assigned each randomised participant a unique identification number that was used throughout the study. All staff, participants, and Biogen Idec personnel involved with the study were masked to treatment apart from safety personnel in the case of serious safety events requiring unmasking as specified in the protocol.

Procedures

Our trial had a screening period of up to 4 weeks before randomisation. Participants attended in-clinic study assessments at baseline (day 1), week 2, and month 2, followed by a monthly study visit schedule alternating between home visits or telephone assessments and in-clinic visits, with the end of study or end of treatment visit done in the clinic if possible (appendix). We allowed housebound participants or those in hospice care to do their study assessments remotely via home nursing visits and telephone contacts. Participants were to remain on assigned double-blind treatment and continue with scheduled assessments for up to 18 months or until the last participant completed the month 12 visit, whichever came first. We aimed to continue nursing visits or telephone contact with participants who discontinued study drug before study completion, to obtain ALSFRS-R scores and to monitor living status, adverse events, and concomitant medications, at least up to the date at which these participants would otherwise have completed the study.

Concomitant drugs, including riluzole, were allowed at the discretion of the investigator, provided that participants already taking riluzole had been on a stable dose for 60 days before day 1 of treatment and planned to continue taking riluzole throughout the study unless discontinued for medical reasons. If initiation of riluzole was deemed necessary, the participant had to be discontinued from the study. Daily vitamins and supplements had to have been stabilised 14 days before day 1 and unchanged during the study. The limit for creatine was set at 5 g per day or less and the limit for vitamin E was set at 1000 IU/day or less.

The primary endpoint of EMPOWER was the CAFS, a joint-rank test that analyses functional outcomes adjusted for mortality.[19,20] Details are published elsewhere but, briefly, the CAFS ranks participants' outcomes on the basis of time to death or change from baseline in ALSFRS-R scores by use of follow-up data to 12 months.[19] We ranked participants who died on the basis of time to death, with earlier time to death ranked the worst. Participants who survived were ranked higher than were

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those who died, based on the change from baseline to endpoint in ALSFRS-R total score, with largest negative changes ranked worst.

We analysed secondary endpoints with all available data up to 18 months, unless otherwise stated, including the following analyses: time to death or respiratory insufficiency (DRI; defined as tracheostomy or the use of non-invasive ventilation for ≥22 h per day for ≥10 consecutive days); time to death; respiratory decline (time to reach ≤50% of predicted upright slow vital capacity or death); change in muscle strength measurements, determined by the overall mega-score for handheld dynamometry to 12 months; quality of life assessed using the five-item form of the amyotrophic lateral sclerosis assessment questionnaire (ALSAQ-5)[22] and analysed as the change from baseline; population pharmacokinetics; and safety. Safety assessments included physical examinations, clinical laboratory evaluations, vital signs, and adverse event (AE) and serious adverse event (SAE) monitoring. Because cases of reversible neutropenia were reported in the phase 2 study with dexpramipexole, we did monthly blood draws (in-clinic alternating with home visits) and assessed absolute neutrophil counts. Neutropenia was managed as shown in the appendix.

Extensive training on all aspects of the trial, including certification in the assessment of key outcomes was provided by Biogen Idec and an outcomes assessment team at the State University of New York (Syracuse, NY, USA) to personnel participating at each site.

Statistical analysis

Our study was powered to independently assess a potential benefit of dexpramipexole compared with placebo on ALSFRS-R total scores and survival. We based the analysis of the CAFS primary endpoint on the efficacy population, defined as all randomly allocated participants who had received at least one dose of study drug and had at least one post-dosing efficacy evaluation or who died during the study. We also assessed the components of the CAFS, ALSFRS-R, and time to death up to 12 months in the same population.

A sample size of 402 participants per group was needed to provide 90% power to detect a mean difference between groups of 2·13 on ALSFRS-R total score at 12 months, assuming a 20% dropout rate. This rate was derived from an assessment of dropout rates of several large trials of amyotrophic lateral sclerosis that were done since 1996 that showed that dropout rate in placebo groups was about 20% per year (appendix). The power calculation used a two-sided Wilcoxon test with $\alpha=0\cdot05$ and an SD of 8·1. The SD was based on the results of the dexpramipexole phase 2 study and published studies of minocycline[23] and glatiramer acetate,[24] which was regarded as representative of the present care of individuals with amyotrophic lateral sclerosis and their associated disease progression rates. For the survival analysis, the study was powered to have an 80% probability for detection of a 37% reduction in the hazard ratio between dexpramipexole and placebo, based on a sample size of 402 participants per treatment group and

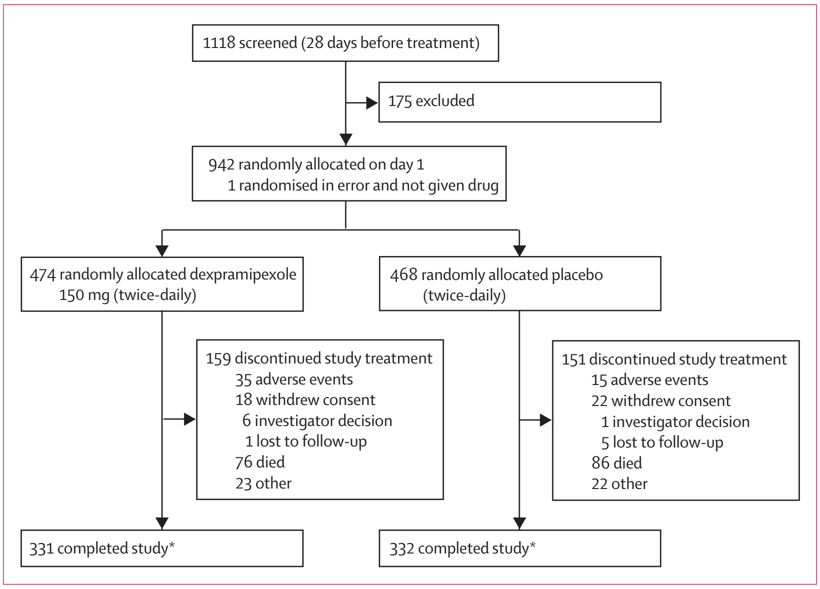


Figure 1: Study profile
*Includes participants who discontinued treatment but completed the study assessments (16 in the dexpramipexole group and 15 in the placebo group).

	Dexpramipexole group (n=474)	Placebo group (n=468)	Overall (N=942)*
Age, years	56·8 (11·3)	57·3 (11·3)	57·1 (11·3)
Sex			
Male	307 (65%)	298 (64%)	605 (64%)
Female	167 (35%)	170 (36%)	337 (36%)
Bodyweight, kg			
Data available	471 (99%)	465 (99%)	936 (99%)
Mean	77·21 (15·0)	77·76 (16·0)	77·48 (15·5)
Body-mass index, kg/m²	26 (4·2)	26·2 (4·3)	26·1 (4·3)
Ethnic group			
White	450 (95%)	439 (94%)	889 (94%)
Asian	4 (<1%)	7 (1%)	11 (1%)
Black	3 (<1%)	10 (2%)	13 (1%)
Not reported	9 (2%)	7 (1%)	16 (2%)
Other	8 (2%)	5 (1%)	13 (1%)
Duration of symptoms, months	14·9 (5·3)	15·5 (5·4)	15·2 (5·3)
Time from diagnosis to baseline, months	7·2 (4·7)	7·6 (5·0)	7·4 (4·9)
Bulbar onset	107 (23%)	112 (24%)	219 (23%)
Family history of amyotrophic lateral sclerosis	33 (7%)	26 (6%)	59 (6%)
Baseline ALSFRS-R score	38·4 (5·2)	37·9 (5·7)	38·2 (5·5)
Predicted upright SVC at baseline	89 (17·6)	89·1 (17·7)	89·1 (17·6)
Concomitant riluzole use	359 (76%)	349 (75%)	708 (75%)

Data are mean (SD) or n (%). *Intention-to-treat population; includes five participants with possible or probable amyotrophic lateral sclerosis who were ultimately diagnosed with a different neurodegenerative disease. ALSFRS-R=amyotrophic lateral sclerosis functional rating scale—revised. SVC=slow vital capacity.

Table 1: Baseline characteristics

an α=0·05. We regarded a hazard ratio reduction of 37% as a clinically meaningful survival benefit. Study recruitment was faster than expected, resulting in a mean follow-up time that was slightly shorter than anticipated. However, because the study enrolled a greater number of participants than intended owing to the rapid enrolment rate, the actual study power calculation used to assess the prespecified endpoints was at least 90%.

For the primary endpoint analysis, we assessed CAFS ranks of data for 12 months of treatment with an ANCOVA model with treatment as a fixed effect, adjusted for baseline ALSFRS-R total score, duration from symptom onset to the first dose of study treatment, site of onset (bulbar or other), and use of riluzole as baseline covariates. A generalised Gehan-Wilcoxon rank test was done as a supportive analysis.

We analysed secondary endpoints in the intention-to-treat population, defined as randomly allocated participants who received at least one dose of study drug. Efficacy comparisons were two-sided statistical tests with α=0·05 for the primary (the CAFS) and secondary endpoints. We also analysed the primary and secondary endpoints in a per-protocol population—defined as the efficacy population without major deviations—as supportive analyses.

To aid in the clinical interpretation of the CAFS, we also analysed its components. We analysed change from baseline in ALSFRS-R total score up to 12 months by use of a mixed-effects repeated-measures model. The model included terms for treatment, time, treatment by time interaction, baseline, and baseline by time interaction and was adjusted for the following covariates: duration from symptom onset to first dose, site of onset, and concomitant use of riluzole. The mixed-effects slope model was not proposed as the primary analysis because this model assumes linearity in the decline of function over time, which might or might not be reported in a study of 12–18 months' duration[25] and, moreover, assumed that all discontinuations were random and non-informative, which is not the case for deaths. We analysed time to death up to 12 months with the Cox proportional hazards model, adjusting for the same covariates used in the CAFS ANCOVA, and generated Kaplan-Meier survival plots.

For the ALSFRS-R component of the CAFS, we used a comparison of the last available observation for a participant with observations from participants at a similar timepoint for ranking purposes when a participant discontinued early. We did additional sensitivity analyses to assess the effect of missing data on the ALSFRS-R. For time-to-event analyses, missing data were censored.

We ranked secondary endpoints in order of importance (time to DRI, time to death, respiratory decline, change in handheld dynamometry, and then change in ALSAQ-5) and used a sequentially closed testing procedure (assessment of endpoints sequentially from the primary through the list of secondary endpoints as defined in the protocol) to control the overall type I error rate due to multiple comparisons of secondary endpoints.

This study is registered with ClinicalTrials.gov, number NCT01281189.

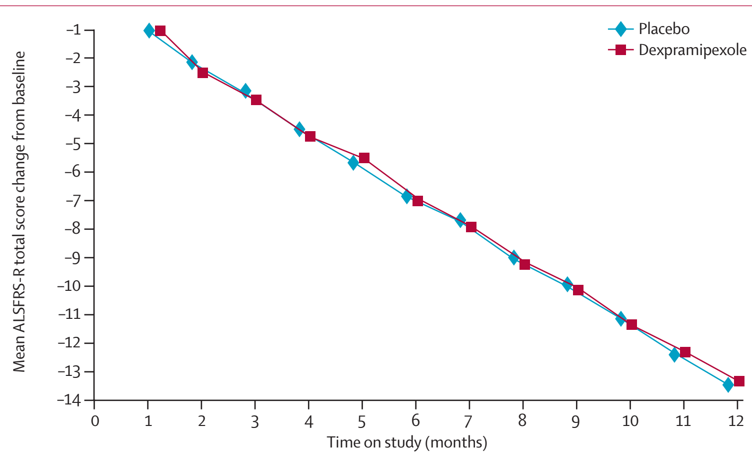
Role of the funding source

The study sponsor (Biogen Idec) was involved in the design and conduct of the study (collection and analysis of data), generation of the statistical tables, and interpretation of this study. All authors had access to the data table listings (prepared by Biogen Idec), which were used to prepare the results section of this report and the corresponding author had full access to all of the data in

	Dexpramipexole group (n=474)	Placebo group (n=468)
Any adverse event	459 (97%)	447 (96%)
Common adverse events*		
Constipation	129 (27%)	109 (23%)
Nausea	106 (22%)	65 (14%)
Weight decrease	75 (16%)	48 (10%)
Insomnia	71 (15%)	60 (13%)
Muscular weakness	64 (14%)	44 (9%)
Cough	45 (9%)	30 (6%)
Dizziness	42 (9%)	28 (6%)
Dry mouth	41 (9%)	20 (4%)
Neutropenia	37 (8%)	8 (2%)
Upper respiratory tract infection	30 (6%)	17 (4%)
Neck pain	24 (5%)	9 (2%)
Serious adverse events	225 (47%)	233 (50%)
Adverse events leading to treatment discontinuation	50 (11%)	36 (8%)
Deaths	92 (19%)	104 (22%)

*Occurring in ≥5% of participants receiving dexpramipexole and at least 2% more frequently than in participants receiving placebo.

Table 2: **Safety profile**



Number of participants												
Placebo	441	456	444	441	434	429	416	413	393	388	366	359
Dexpramipexole	435	459	456	447	430	420	409	402	389	369	365	357

Figure 2: **Change from baseline in ALSFRS-R total score by 12 months (mixed-effects repeated measures model over time)**
ALSFRS-R=amyotrophic lateral sclerosis functional rating scale—revised.

	Dexpramipexole group (n=474)	Placebo group (n=468)	HR or LS difference (95% CI)	p value
Time to death or respiratory impairment ≤18 months				
Participants*	113 (24%)	121 (26%)	HR 1·04 (0·80 to 1·35)	0·77
Time to event for 20th percentile, months	12·35	12·06	..	
Time to death ≤18 months				
Participants*	97 (20%)	108 (23%)	HR 0·98 (0·75 to 1·3)	0·90
Time to event for 20th percentile, months	13·08	13·34	..	
Time to reach ≤50% predicted upright SVC or death				
Participants	173 (36%)	196 (42%)	HR 0·97 (0·79 to 1·19)	0·77
Time to event, 50th percentile, months	16·0	14·1	..	
HHD megascore change from baseline at 12 months	–0·73 (–0·78 to –0·67)	–0·70 (–0·76 to –0·65)	LS difference –0·02 (95% CI –0·09 to 0·05)	0·56
ALSAQ-5 total score change from baseline at 12 months	21·17 (18·98 to 23·37)	21·35 (19·23 to 23·48)	LS difference –0·18 (95% CI –2·95 to 2·58)	0·90

Data are n (%) or mean (SD), unless otherwise stated. HR=hazard ratio. LS=least squares. SVC=slow vital capacity. HHD=handheld dynamometry (tested on nine muscle groups: shoulder, elbow, hip, and knee flexion; elbow, knee, and wrist extension; first interosseous contraction; and ankle dorsiflexion). ALSAQ-5=five-item amyotrophic lateral sclerosis assessment questionnaire (higher scores show worse quality of life). *Includes post-discontinuation data up to 18 months.

Table 3: **Secondary efficacy endpoints**

the study. The first draft of the report was prepared, with financial support from Biogen Idec, by Aruna Seth (Excel Scientific Solutions, Southport, CT, USA), and Biogen Idec reviewed and provided feedback on the report to the authors. Biogen Idec authors in conjunction with co-authors made the decision to submit this report for publication and the corresponding author takes final responsibility for this decision.

Results

We enrolled 943 participants between March 28, 2011, and Sept 30, 2011 (figure 1). Table 1 shows baseline charcteristics. Enrolment rates varied between participating study sites (0·25–6·45 participants per centre per month). The mean time from screening to baseline visit was 14·87 (range 1–28) days. Of 942 participants randomly allocated treatment and who received at least one dose of allocated drug, 632 (67%) completed the study treatment (figure 1). Most discontinuations from treatment in both groups were because of death, with more study participants discontinuing from the dexpramipexole group because of AEs (table 2). All other reasons for discontinuation were similar in both groups (figure 1).

The least-squares mean CAFS score at 12 months for participants in the dexpramipexole group was 441·76 (95% CI 415·43–468·08), which did not differ from the score for participants in the placebo group of 438·84 (412·81–464·88; p=0·86). At 12 months, we noted no differences in mean change from baseline in ALSFRS-R total score at 12 months (–13·34 in the dexpramipexole group *vs* –13·42 in the placebo group; p=0·90) or time to death (74 [16%] *vs* 79 [17%]; hazard ratio 1·03 [0·75–1·43]; p=0·84). We noted a similar change from baseline in ALSFRS-R total score in both groups at all assessments up to 12 months (figure 2), and no difference between groups in the per-protocol population (data not shown).

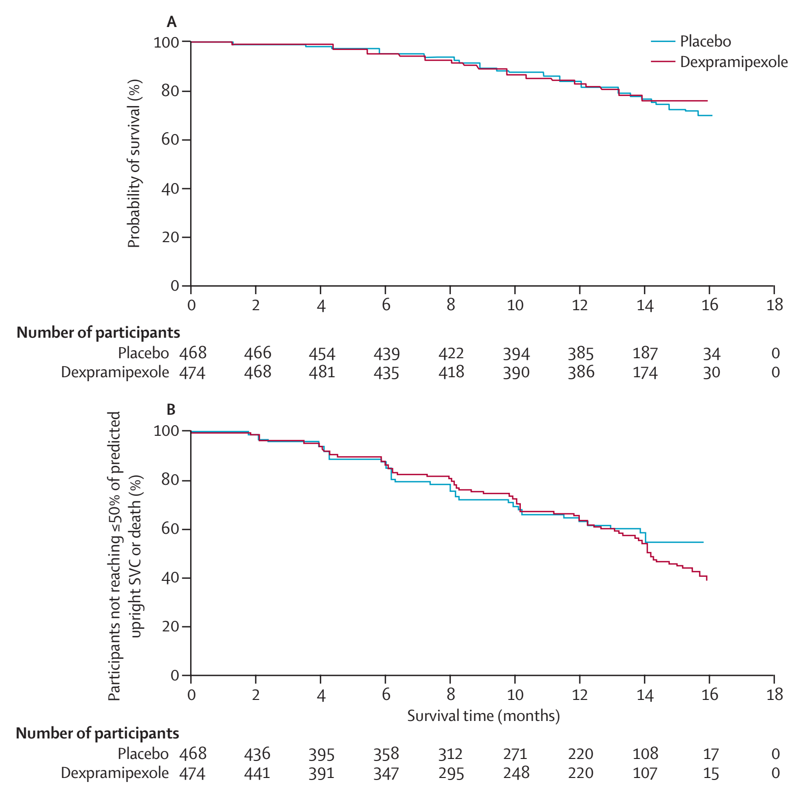


Figure 3: **Kaplan-Meier analyses of survival time ≤18 months (A) and time to reach ≤50% slow vital capacity or death (B)**

The absence of efficacy of dexpramipexole up to 12 months was confirmed by the results of key secondary endpoints (table 3).

During 18 months of follow-up, we noted no significant differences between the dexpramipexole and placebo groups in time to DRI, time to death alone (figure 3), and respiratory decline (time to reach ≤50% of predicted upright slow vital capacity or death); equally, during 12 months of follow-up, we noted no significant differences in the change in overall handheld dynamometry scores, or change from baseline in ALSAQ-5 total score (table 3), or in a tertiary endpoint of change in upright slow vital capacity (least-squares mean difference between groups 0·81; 95% CI –2·93 to 4·55; p=0·67). In the prespecified subgroup analyses (including treatment by age, sex, and site of onset; appendix), none of the comparisons was significantly different between groups (data not shown).

To ensure that drug exposure had been achieved, we assessed all available pharmacokinetic samples from 417 participants in the dexpramipexole group. These analyses confirmed the presence of dexpramipexole and suggested that drug concentrations were similar as those reported in the phase 2 study[18] (data not shown). In addition, the absence of dexpramipexole was confirmed in 50 samples from participants who received placebo. A formal population pharmacokinetic analysis was not done.

Dexpramipexole was generally well tolerated and safety seemed equivalent to that in the phase 2 study.[18] Overall, incidences of SAEs, treatment discontinuations due to AEs, study withdrawals due to AEs, and deaths reported in both groups were similar (table 2). More participants withdrew in the dexpramipexole group than in the placebo group. The most common AEs (occurring in at least 5% of the dexpramipexole group and with at least 2% more frequency than in the placebo group) were constipation, nausea, weight loss, insomnia, and muscular weakness (table 2). Incidence of neutropenia was higher in participants treated with dexpramipexole than in the placebo group. This neutropenia was reversible in all but one participant (ie, in seven of eight participants) in the placebo group and four participants (ie, not reversible in four of 37 participants who had neutropenia) in the dexpramipexole group. Of these five participants, one died and the others withdrew consent before the resolution of neutropenia. The death occurred in a participant who was receiving dexpramipexole, and was regarded by the local investigator and the sponsor (Biogen Idec) as related to end-stage motor neuron disease and unrelated to dexpramipexole treatment.

Mean treatment compliance was 95·3% (SD 9·2) in the dexpramipexole group and 97·2% (5·8) in the placebo group (appendix).

Discussion

EMPOWER was a large phase 3 international study that assessed a novel outcome measure (the CAFS) to investigate the efficacy and safety of dexpramipexole in amyotrophic lateral sclerosis (panel). Although rare events of neutropenia and severe neutropenia were more common in dexpramipexole-treated participants, dexpramipexole was generally well tolerated but it was not efficacious compared with placebo on the primary endpoint or key secondary endpoints.

With the negative efficacy results of this phase 3 study, dexpramipexole joins the list of compounds that have not shown efficacy in amyotrophic lateral sclerosis in phase 3 studies, despite early indications of potential efficacy in small pilot or phase 2 studies. For example, early reports of a beneficial effect of lithium from a small non-placebo-controlled study[26] were not confirmed.[27–29] A small phase 2 study of talampanel did not show significant differences from placebo, although non-significant changes in group mean ALSFRS-R total scores and muscle strength at endpoint were reported in a completer's analysis.[30] Talampanel subsequently failed to show any treatment effects in a large phase 3 study in amyotrophic lateral sclerosis.[31] Most recently, a phase 2 study of ceftriaxone in amyotrophic lateral sclerosis reported a 38% improvement in function, but the phase 3 study was stopped early by the data review board because ceftriaxone treatment was regarded as unlikely to show any difference from placebo on the primary efficacy measures of survival or symptom progression in amyotrophic lateral sclerosis.[32]

Overall, these results underscore the challenges in the use of phase 2 studies to predict phase 3 studies in amyotrophic lateral sclerosis. Small phase 2 studies might have little predictive validity for both appropriate dose selection and effect size for phase 3 trials; alternatively, phase 3 trials in amyotrophic lateral sclerosis to date might have enrolled a broader, more heterogeneous patient sample than the focused signal-generating populations studied in phase 2 trials.

Reviews of the challenges in the design of phase 2 studies have been published previously.[33–35] These challenges include the absence of understanding of the underlying biology and targets for intervention, the absence of a biomarker that is indicative of the biological activity of an investigational agent, selection of appropriate dose, the absence of a disease model that can be used to identify candidates for study, inadequate sample sizes, and disease heterogeneity. These challenges have thus far been inadequately addressed, hence almost all phase 3 studies in amyotrophic lateral sclerosis to date have not met their primary endpoints.[35] One solution might be to do several phase 2 studies to ensure that answers to the aforementioned challenges have been obtained before embarking on a phase 3 study.[35] Likewise, the use of a biomarker could help identify appropriate populations of patients for whom some drugs might be useful, thereby enrolling more enriched phase 3 study populations.[36]

EMPOWER was designed to replicate the phase 2 study of dexpramipexole; accordingly, the inclusion and exclusion criteria for EMPOWER were largely identical to those used in the phase 2 trial. In a post-hoc analysis,

Panel: Research in context

Systematic review

We searched PubMed for randomised placebo-controlled studies of dexpramipexole in amyotrophic lateral sclerosis published in English before Dec 31, 2012, with the search terms "dexpramipexole", "amyotrophic lateral sclerosis", and "clinical trials." The only dexpramipexole publication retrieved was the phase 2 study.[18] We also identified other recently published phase 2 studies of drugs that have shown promise in amyotrophic lateral sclerosis, including lithium[26] and talampanel.[27]

Interpretation

In this randomised, placebo-controlled, phase 3 study we used the combined assessment of function and survival (the CAFS) to explore the efficacy and safety of dexpramipexole for the treatment of ALS. We also analysed the components of the CAFS, change from baseline in ALSFRS-R total score, and rates of survival. Compared with placebo, dexpramipexole treatment did not differ significantly in any of these measures, suggesting that at the dose tested in this study dexpramipexole was not effective in the population tested. On the basis of the sample size and number of endpoints included in the study, EMPOWER is the most comprehensive trial of amyotrophic lateral sclerosis to date. EMPOWER has collected a robust clinical database that has contributed to the Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials (PROACT) database. EMPOWER established a new endpoint that combined function and survival. Future studies can consider the use of the CAFS to assess the differential effects of potential treatments. Lessons learned from the design and conduct of EMPOWER will serve to inform future clinical research strategies in amyotrophic lateral sclerosis—eg, in choice of phase 2 and phase 3 study designs (endpoints and sample size) and in approaches that might be used to increase recruitment, retention, and follow-up of participants who drop out of the study, to ensure that the collection of data is as complete as possible.

baseline ALSFRS-R total score, age, site of onset and sex of participants enrolled in EMPOWER were similar to those who had been enrolled in the phase 2 study, but differences were noted in riluzole use (708 [75%] participants in the phase 3 trial *vs* 62 [61%] in the phase 2 trial; p=0·0018), participants with definite amyotrophic lateral sclerosis by El Escorial criteria (303 [32%] *vs* 47 [46%]; p=0·0047), and symptom duration (15·2 months *vs* 14·0 months; p=0·0362). Based on these post-hoc analyses, subsequent research will be done to establish what effect these differences could have had on the study results.

Participant enrolment in EMPOWER was faster than that reported in previous phase 3 trials, perhaps because of the intense interest in potential treatments of individuals with amyotrophic lateral sclerosis and their care providers, in view of the high unmet need for effective therapies and an awareness of the encouraging results of the phase 2 study. By contrast with many other phase 3 studies, EMPOWER included participants with possible amyotrophic lateral sclerosis. Historically, the inclusion of participants in phase 3 clinical trials has been restricted to those who have laboratory-supported probable, probable, or definite disease, in accordance with the revised El Escorial criteria.[21] The inclusion of those participants with possible amyotrophic lateral sclerosis faciliated enrolment of participants with less severe disease. Diagnosis of participants with milder disease was largely accurate. However, five participants enrolled in EMPOWER with possible or probable amyotrophic lateral sclerosis were ultimately diagnosed with a neurodegenerative disease other than amyotrophic lateral sclerosis; they were included in the efficacy and intention-to-treat analyses but not the per-protocol analyses.

To our knowledge, for the first time in a phase 3 study of amyotrophic lateral sclerosis we analysed function and survival in a combined assessment as the primary endpoint (appendix). This feature, piloted in the phase 2 study of dexpramipexole, was used to address the challenge noted in trials of other potential treatments of amyotrophic lateral sclerosis of how to account for mortality when analysing functional outcome measures.

Contributors

MEC participated in the study design and protocol development, study leadership, and data collection and interpretation. LHvdB, JMS, HM, JSM, AL, and OH participated in the study design and protocol development, assessment of participants, and data collection and interpretation. MEB and DA participated in the study design and protocol development, selection of the combined assessment of function and survival (the CAFS) as the primary endpoint, statistical analysis plan, and data analysis and interpretation. EWI participated in the study design and protocol development, selection of the CAFS as primary endpoint, and statistical analysis plan. ALM participated in the statistical analysis plan and data analysis. YD participated in the study design and protocol development, statistical analysis plan, selection of the CAFS as the primary endpoint, and data analysis. WRF participated in the study design and protocol development, statistical analysis plan, and data analysis and interpretation. DAK participated in the study design and protocol development, statistical analysis plan, selection of the CAFS as the primary endpoint, and data analysis and interpretation. All authors provided input in and content of this manuscript before the report was written, reviewed and edited all drafts of this report, provided approval for the final report before submission, and had full editorial control of the paper.

For the **PROACT database** see https://nctu.partners.org/ProACT

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Conflicts of interest

MEC was the principal investigator of this study and has received a grant from Biogen Idec for this role. In the past 5 years, MEC has served as a consultant for Teva Pharmaceuticals, GlaxoSmithKline, Millenium, Synapse (data safety monitoring board, DSMB), Ono (DSMB), Link Medicine, and Trophos (DSMB) and has served on an advisory board for Biogen Idec. LHvdB was a study investigator and has served on an advisory board for Biogen Idec and Cytokinetics and as a consultant for Baxter. JMS was a study investigator and has received research funding from the National Institutes of Health, ALS Association, Muscular Dystrophy Association, ALS Therapy Alliance, Biogen Idec, Cytokinetics, GlaxoSmithKline, Sanofi-Aventis, Neuraltus, Teva Pharmaceuticals, and ISIS. JMS has received personal compensation for consulting from Biogen Idec, Cytokinetics, GlaxoSmithKline, Teva Pharmaceuticals, ISIS, and Trophos. HM was a study investigator and received grants from Avanir, Knopp Biosciences, Biogen Idec, and Cytokinetics for clinical trials and honoraria for participating in advisory board meetings from Avanir, Sanofi-Aventis, Shionogi, and Biogen Idec. HM is now a member of the DSMB for the NeuralStem clinical trials (sponsored by NeuralStem, NCT NCT01730716 and NCT01348451). HM received honoraria from Sanofi-Aventis Japan for giving seminars at the annual meetings of the Japanese Neurological Society in 2009 and 2010, and received a conference grant (to Columbia University) for the 2011 International ALS Conference from the National Institute of Neurological Disorders and Stroke, the US National Institutes of Health's Office of Rare Diseases Research, Muscular Dystrophy Association, ALS Association, ALS Society of Canada, Adams Foundation, Ride for Life, ALS Hope Foundation, Les Turner Foundation, Sanofi-Aventis, Biogen Idec, Knopp Biosciences, and Avania. JSM was a study investigator and has served on an advisory board for Biogen Idec and on scientific committees for the recent ALS trials by Teva Pharmaceuticals (talampanel) and Trophos (olesoxime). AL received consulting fees and travel support from Biogen Idec and Teva Pharmaceuticals, consulting fees from Lundbeck, Knopp Biosciences, GlaxoSmithKline, and Boehringer Ingelheim, speaker's honoraria from Biogen Idec and Merz. OH received honoraria for serving in a DSMB for Ono and for serving on scientific advisory panels for Sanofi-Aventis and Biogen Idec. OH also has received honoraria from Merck Serono and Schering. MEB and DA are employees of Knopp Biosciences. EWI is an independent consultant and was employed at Knopp Biosciences when this trial was conducted. ALM, YD, WRF, and DAK are employees of Biogen Idec.

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References

1 National Institute of Neurological Disorders and Stroke, National Insitutes of Health. Amyotrophic lateral sclerosis (ALS) fact sheet. http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm (accessed April 15, 2013).

2 Rowland LP, Schneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; **344:** 1688–700.

3 Bruijn LI, Cudkowicz M. Therapeutic targets for amyotrophic lateral sclerosis: current treatments and prospects for more effective therapies. *Expert Rev Neurother* 2006; **6:** 417–28.

4 Cozzolino M, Ferri A, Carri MT. Amyotrophic lateral sclerosis: from current developments in the laboratory to clinical implications. *Antioxid Redox Signal* 2008; **10:** 405–43.

5 Morren JA, Galvez-Jimenez N. Current and prospective disease-modifying therapies for amyotrophic lateral sclerosis. *Expert Opin Investig Drugs* 2012; **21:** 297–320.

6 Bensimon G, Lacomblez L, Meininger V, ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Engl J Med* 1994; **330:** 585–91.

7 Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996; **347:** 1425–31.

8 Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012; **3:** CD001447.

9 Atsumi T. The ultrastructure of intramuscular nerves in amyotrophic lateral sclerosis. *Acta Neuropathol* 1981; **55:** 193–98.

10 Sasaki S, Iwata M. Impairment of fast axonal transport in the proximal axons of anterior horn neurons in amyotrophic lateral sclerosis. *Neurology* 1996; **47:** 535–40.

11 Siklós L, Engelhardt J, Harati Y, Smith RG, Joó F, Appel SH. Ultrastructural evidence for altered calcium in motor nerve terminals in amyotropic lateral sclerosis. *Ann Neurol* 1996; **39:** 203–16.

12 Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 2006; **443:** 787–95.

13 Lee J, Boo JH, Ryu H. The failure of mitochondria leads to neurodegeneration: do mitochondria need a jump start? *Adv Drug Deliv Rev* 2009; **61:** 1316–23.

14 Moreira PI, Zhu X, Wang X, et al. Mitochondria: a therapeutic target in neurodegeneration. *Biochim Biophys Acta* 2010; **1802:** 212–20.

15 Cheah BC, Kiernan MC. Dexpramipexole, the R(+) enantiomer of pramipexole, for the potential treatment of amyotrophic lateral sclerosis. *IDrugs* 2010; **13:** 911–20.

16 Alavian KN, Dworetzky SI, Bonanni L, et al. Effects of dexpramipexole on brain mitochondrial conductances and cellular bioenergetic efficiency. *Brain Res* 2012; **1446:** 1–11.

17 Danzeisen R, Schwalenstoecker B, Gillardon F, et al. Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer SND919CL2x [(+)2-amino-4,5,6,7-tetrahydro-6-Lpropylamino-benzathiazole dihydrochloride]. *J Pharmacol Exp Ther* 2006; **316:** 189–99.

18 Cudkowicz M, Bozik ME, Ingersoll EW, et al. The effects of dexpramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis. *Nat Med* 2011; **17:** 1652–56.

19 Berry JD, Miller R, Moore DH, et al. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials. *Amyotroph Lateral Scler Frontotemporal Degener* 2013; **14:** 162–68.

20 Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med* 1999; **18:** 1341–54.

21 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; **1:** 293–99.

22 Gołąb-Janowska M, Honczarenko K, Stankiewicz J. Usefulness of the ALSAQ-5 scale in evaluation of quality of life in amyotrophic lateral sclerosis. *Neurol Neurochir Pol* 2010; **44:** 560–66.

23 Gordon PH, Moore DH, Miller RG, et al, for the Western ALS Study Group. Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial. *Lancet Neurol* 2007; **6:** 1045–53.

24 Meininger V, Drory V, Leigh P, Ludolph A, Robberecht W, Silani V. Glatiramer acetate has no impact on disease progression in ALS at 40 mg/day: a double-blind, randomized, multicentre, placebo-controlled trial. *Amyotroph Lateral Scler* 2009; **10:** 378–83.

25 Gordon PH, Cheng B, Salachas F, et al. Progression in ALS is not linear but is curvilinear. *J Neurol* 2010; **257:** 1713–17.

26 Fornai F, Longone P, Cafaro L, et al. Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci* 2008; **105:** 2052–57.

27 Verstraete E, Veldink JH, Huisman MH, et al. Lithium lacks effect on survival in amyotrophic lateral sclerosis: a phase IIb randomised sequential trial. *J Neurol Neurosurg Psychiatry* 2012; **83:** 557–64.

28 Morrison KE, Dhariwal S, Hornabrook R, et al. Lithium in patients with amyotrophic lateral sclerosis (LiCALS): a phase 3 multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2013; **12:** 339–45.

29 Aggarwal SP, Zinman L, Simpson E, et al, and the Northeast and Canadian Amyotrophic Lateral Sclerosis consortia. Safety and efficacy of lithium in combination with riluzole for treatment of amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010; **9:** 481–88.

30 Pascuzzi RM, Shefner J, Chappell AS, et al. A phase II trial of talampanel in subjects with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2010; **11:** 266–71.

31 Shefner J, Meininger V, Talampanel ALS Study Group. Results of a clinical trial of talampanel in patients with ALS. *Amyotroph Lateral Scler* 2011; **11:** 44–45.

32 Cudkowicz M, Shefner J, NEALS Consortium. Stage 3 clinical trial of ceftriaxone in subjects with ALS. *Neurology* 2013; **80** (suppl 36)**:** abstr 001.

33 Aggarwal S and Cudkowicz M. ALS drug development: reflections from the past and a way forward. *Neurotherapeutics* 2008;**5:** 516–27.

34 Shefner JM. Designing clinical trials in amyotrophic lateral sclerosis. *Phys Med Rehabil Clin N Am* 2008; **19:** 495–508.

35 Cudkowicz ME, Katz J, Moore DH, et al. Toward more efficient clinical trials for amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2010; **11:** 259–65.

36 Turner MR, Hardiman O, Benatar M, et al. Controversies and priorities in amyotrophic lateral sclerosis. *Lancet Neurol* 2013; **12:** 310–22.