RESEARCH PAPER

Ultra-high-dose methylcobalamin in amyotrophic lateral sclerosis: a long-term phase II/III randomised controlled study

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ABSTRACT

Objective To evaluate the efficacy and safety of intramuscular ultra-high-dose methylcobalamin in patients with amyotrophic lateral sclerosis (ALS).

Methods 373 patients with ALS (El Escorial definite or probable; laboratory-supported probable; duration ≤36 months) were randomly assigned to placebo, 25 mg or 50 mg of methylcobalamin groups. The primary endpoints were the time interval to primary events (death or full ventilation support) and changes in the Revised ALS Functional Rating Scale (ALSFRS-R) score from baseline to week 182. Efficacy was also evaluated using post-hoc analyses in patients diagnosed early (entered ≤12 months after symptom onset).

Results No significant differences were detected in either primary endpoint (minimal p value=0.087). However, post-hoc analyses of methylcobalamin-treated patients diagnosed and entered early (≤12 months' duration) showed longer time intervals to the primary event (p<0.025) and less decreases in the ALSFRS-R score (p=0.025) than the placebo group. The incidence of treatment-related adverse events was similar and low in all groups.

Conclusion Although ultra-high-dose methylcobalamin did not show significant efficacy in the whole cohort, this treatment may prolong survival and retard symptomatic progression without major side effects if started early.

Trial registration number NCT00444613.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is an intractable neurodegenerative disease characterised by motor neuron degeneration typically presenting with muscle weakness and atrophy.1 Respiratory failure due to muscle weakness is the major cause of death. Without mechanical ventilation support, patients succumb to this disease within 3–6 years from its onset.

The widely used drug for ALS, riluzole, provides modest prolongation of survival (2–3 months), but no beneficial effects were shown on muscle strength and little on bulbar function.2 Moreover, safety concerns, such as liver dysfunction, exist.3 Edaravone has been approved for retarding the clinical deterioration of ALS, but its effect on the survival is unknown.4

The deficiency in vitamin B₁₂ is associated with central nervous system lesions including subacute combined degeneration of the cord, indicating an important function of B₁₂ in the spinal cord and the brain. Methylcobalamin, an active vitamin B₁₂, used in Japan to treat peripheral neuropathy and megaloblastic anaemia, is a potential candidate for ALS treatment. It functions as a coenzyme for homocysteine remethylation as a methyl donor, and inhibits neuronal degeneration by decreasing levels of homocysteine, the accumulation of which contributes to neuronal degeneration in patients with ALS.5,6 It also activates extracellular signal-regulated kinases 1 and 2 and Akt to induce neurite outgrowth and prolong neuronal survival.7 Cyanates/cyanide conjugates of B₁₂ are not acting as methyl donor and have not been proven to show these effects.

Preclinical studies have reported that methylcobalamin protects neurons against glutamate neurotoxicity8 and promotes nerve regeneration.9 It has also been shown that intraperitoneal ultra-high dosage inhibits disease progression in a wobbler mouse.10 Oral administration in high dose would be ineffective because of the limited availability of the gastric intrinsic factor for its absorption. Clinical studies have demonstrated the efficacy of intramuscular ultra-high-dose methylcobalamin on compound muscle action potentials.11 Moreover, a small-sized study has demonstrated that, if started early in the disease course, ultra-high-dose methylcobalamin prolongs ventilation-free survival.12

Based on these results, we conducted a long-term phase II/III clinical trial to evaluate the efficacy and safety of intramuscular ultra-high-dose methylcobalamin in Japanese patients with ALS.

METHODS

This multicentre, randomised, double-blind, placebo-controlled clinical trial was conducted from December 2006 to March 2014 at 51 sites in Japan.

Patients

Patients satisfying the following inclusion criteria were eligible: outpatients aged 20 years or older; clinically definite, clinically probable, or clinically probable, laboratory-supported ALS diagnosis according to the revised El Escorial criteria (Airlie House criteria)13; duration from the symptom onset...
Questionnaire

and the quality of life evaluated using the ALS Assessment

respiratory function assessed using %FVC, grip strength,

multiple conduction blocks, new start or change in the dose or
cardiovascular, renal, hepatic disease or any haematolog-

serious cardiovascular, renal, hepatic disease or any haematolog-

tation, per cent-predicted forced vital capacity (%FVC) ≤60%,

other than twitching or cramping of muscles. The key exclusion

the patient recognised weakness or any other motor symptoms

score decrease by 1–3 points during the 12-week observa-
tion period. The definition of onset was the initial time that

progression of disability by measuring respiratory function and

system); and Revised ALS Functional Rating Scale (ALSFRS-R)

of daily living; and 5, bedridden status requiring a life support

social life; 4, requirement of constant assistance in all aspects

events; however, all deaths were counted as adverse events
due to the progression of ALS were not counted as adverse

The primary and secondary efficacy endpoints were evalu-

were simultaneously evaluated using contrast coefficients to

Methylcobalamin efficacy and dose–response relationships

variables including the interval between symptom onset and
diagnosis (≤12 months, >12 months), gender, %FVC (<90%,
≥90%) and several other variables to explore prognostic factors

for events post hoc. Analyses were performed using SAS V.9.3
software.

RESULTS

A total of 373 patients were enrolled and randomly assigned to
placebo or 25 mg or 50 mg methylcobalamin groups (124, 124
and 125 patients, respectively; figure 1). Exclusion of 3 patients
(1 and 2 patients in the placebo and 50 mg groups, respectively)
for not satisfying the diagnostic criteria yielded 370 patients.
The study was completed by 260 patients, with 113 patients
withdrawn because they declined to participate.

The baseline demographic and disease characteristics were

similar among the groups, without significant differences
(table 1). Approximately half the patients were diagnosed as
having clinically probable ALS (46.2%) and had upper motor
neuron-onset ALS (49.5%). Most of the patients (89.7%) were
having clinically probable ALS (46.2%) and had upper motor


All assessments, except for ECG, were conducted on weeks
0, 4 and 16, and at 12-week intervals thereafter to week 172,
and on week 182. For patients who discontinued therapy due
to the primary event, the last assessment was conducted within
4 weeks of the day the event occurred. Different investiga-
tors were responsible for drug administration, as well as effi-
cacy, ALSFRS-R and safety assessments, to maintain blindness
throughout the study, because the active ingredients in methyl-
cobalamin colour urine red.

The efficacy analyses were conducted using a population anal-

for those patients who received methylcobalamin and had

ed evaluative primary endpoint data based on the intention-to-treat

principle. This was called the full analysis set. The safety analy-

were made on a safety data set composed of those patients

who were evaluated for safety. Missing data from patients who

discontinued methylcobalamin after a primary event were

imputed with the final evaluation data after discontinuation.

Methylcobalamin efficacy and dose–response relationships

were simultaneously evaluated using contrast coefficients to

compare placebo with 50 mg and placebo with all methylco-

balamin groups combined, respectively. The time interval to

the primary event was compared among groups using log-rank

scores, and the changes in the ALSFRS-R score and secondary

endpoint measures were evaluated using the Wilcoxon score
(patients who died or whose data after a primary event were not
collected within 28 days from the event were ranked worst). The

p values for the primary test were adjusted for multiplicity, with

the statistical analysis plan described in online supplementary
e-appendix. In addition, the Cox proportional hazards model
with backward elimination for the placebo group was used with
variables including the interval between symptom onset and
diagnosis (≤12 months, >12 months), gender, %FVC (<90%,
≥90%) and several other variables to explore prognostic factors

for events post hoc. Analyses were performed using SAS V.9.3
software.

Outcome measures

The primary endpoints were the time to primary events and

the change in ALSFRS-R score from baseline to week 182. The

primary events were defined as death by any cause or invasive

or non-invasive ventilation support ≥22 hours per day due to

ALS progression. On the occurrence of a primary event, treat-

ment was discontinued. ALSFRS-R quantitatively evaluates the

progression of disability by measuring respiratory function and

physical ability in daily living.

The secondary endpoints included muscle strength assessed
using the manual muscle test (Medical Research Council Scale),
physical functional status measured with the Norris Scale, 
respiratory function assessed using %FVC, grip strength,
and the quality of life evaluated using the ALS Assessment
Questionnaire.14,15

The primary and secondary efficacy endpoints were evalu-

ated using post-hoc analyses in a subgroup of patients diagnosed
early (at screening ≤12 months after symptom onset) and con-

continued for 182 weeks in a manner that the patients and

their caregivers could not see the formulation colour (the active

ingredients in methylcobalamin colour the formulation red).

Changes in riluzole administration were not allowed. Edaravone
was not used in any of the subjects.

Randomisation and treatment

The patients were centrally randomised to the placebo or 25 mg

or 50 mg methylcobalamin groups using the order of registra-

tion (scores range from 1 to 5: 1 denotes no difficulty in daily

living and working; 2, ability to live or work unaided; 3, require-

ment of assistance in daily living due to incapability of managing

social life; 4, requirement of constant assistance in all aspects

of daily living; and 5, bedridden status requiring a life support

system); and Revised ALS Functional Rating Scale (ALSFRS-R)

score decrease by 1–3 points during the 12-week observa-

tion period. The definition of onset was the initial time that

the patient recognised weakness or any other motor symptoms

other than twitching or cramping of muscles. The key exclusion

criteria were tracheostomy or previous use of non-invasive venti-

lation, per cent-predicted forced vital capacity (%FVC) ≤60%,
multiple conduction blocks, new start or change in the dose or
administration of riluzole after the observation period began, or

serious cardiovascular, renal, hepatic disease or any haematolog-

ical changes suggestive of B12 deficiency.

This report follows the Consolidated Standards of Reporting
Trials guidelines.

Allocated drugs were intramuscularly administered twice per
week starting from the end of the observation period (12 weeks)
and continued for 182 weeks in a manner that the patients and

their caregivers could not see the formulation colour (the active

ingredients in methylcobalamin colour urine red).

Drug safety was evaluated on the incidence of adverse events

throughout the study, because the active ingredients in methyl-

cobalamin colour urine red.
Neuromuscular

Figure 1 Patient flow.

Efficacy

Significant differences were not detected for either primary endpoint; the minimal crude p value was 0.09 for the change in the ALSFRS-R score, and its adjusted value was 0.19 (table 2). The time to the primary event was slightly prolonged in the active treatment groups (HR [95% CI]: 0.83 [0.58 to 1.20] for 25 mg and 0.92 [0.65 to 1.32] for 50 mg methylcobalamin groups). The median time to the primary event was 880 for placebo, 1147 for 25 mg and 954 days for 50 mg methylcobalamin groups (figure 2A). The median change in the ALSFRS-R score from baseline to week 182 decreased in relation to the allocated dose: −24.0 for placebo, −22.0 for 25 mg and −21.0 for 50 mg methylcobalamin groups (figure 2B).

For the secondary endpoints, the median change in manual muscle test and the Norris Scale scores from baseline to week 182 decreased in a dose-dependent manner, although this decrease was not significantly different among the groups (online supplementary table e-1).

Patients diagnosed early (duration ≤12 months)

The post-hoc analysis of the subgroup of patients diagnosed early (diagnosed with ALS ≤12 months after symptom onset) demonstrated a significant dose–response-dependent prolongation in time to the primary event (HR [95% CI]: 0.64 [0.38 to 1.09] for 25 mg [p=0.01] and 0.50 [0.27 to 0.93] for 50 mg [p=0.01] methylcobalamin groups). The median time to the primary event (95% CI) was 570 (465 to 720) days for placebo, 1087 (564 to –) days for 25 mg, and 1197 (609 to –) days for 50 mg methylcobalamin groups (table 2, figure 2C).

The change in the ALSFRS-R score also decreased in a dose-dependent manner (the p value for 25 mg was 0.01 and was 0.003 for 50 mg methylcobalamin compared with placebo; figure 2D).

To confirm the validity of the results, the time-related changes in the efficacies on the primary event and on ALSFRS-R scores were analysed; methylcobalamin exhibited efficacy or a trend towards efficacy on primary events in patients diagnosed ≤12 months after symptom onset. Additionally, efficacy or a trend towards efficacy on ALSFRS-R scores was frequently observed in the first 24 months after symptom onset (online supplementary tables e-2 and e-3).

Among the secondary endpoints, a dose–response inhibition in worsening was shown in the Norris Scale score (p values: 0.008 for 25 mg and 0.005 for 50 mg) and %FVC (p values of 0.004 for 25 mg and <0.001 for 50 mg) (online supplementary table e-4).

Patients with other poor prognostic factors

Applying the Cox proportional hazards model with backward elimination to data in the placebo group determined the following poor prognostic factors: diagnostic interval >12 months, being male, %FVC being <90% and being without riluzole (online supplementary table e-5). Methylcobalamin at both 25 mg and 50 mg tended to reduce the HR in men and %FVC <90% (HR, 0.76–0.77; online supplementary table e-6). The decreased ALSFRS-R score (95% CI) in the 50 mg group was 4.3 (0.7 to 7.9; p=0.095) for men and 4.5 (0.9 to 8.1; p=0.020) for %FVC <90% (online supplementary table e-7).

Safety

Adverse events were reported by more than 97% of patients in each group. Treatment-related adverse events were reported with a similar incidence of 4.1% (5/123), 7.3% (9/124) and 5.7% (7/123) in the placebo, 25 mg and 50 mg methylcobalamin groups, respectively. The incidence of serious adverse events was also similar in the placebo, 25 mg and 50 mg methylcobalamin groups: 64.2%, 62.1% and 65.0%, respectively. Of the six patients who died of causes other than ALS progression, the cause of one death in the 50 mg methylcobalamin group was due to cardiac arrest following myocardial infarction or arrhythmia,
Table 1  Baseline characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=123)</th>
<th>Methylcobalamin 25 mg (n=124)</th>
<th>Methylcobalamin 50 mg (n=123)</th>
<th>Overall (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71 (57.7)</td>
<td>81 (65.3)</td>
<td>71 (57.7)</td>
<td>223 (60.3)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (42.3)</td>
<td>43 (34.7)</td>
<td>52 (42.3)</td>
<td>147 (39.7)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>62.2±10.7</td>
<td>60.8±10.1</td>
<td>62.4±9.6</td>
<td>61.8±10.1</td>
</tr>
<tr>
<td>&lt;65</td>
<td>61 (49.6)</td>
<td>77 (62.1)</td>
<td>65 (52.8)</td>
<td>203 (54.9)</td>
</tr>
<tr>
<td>≥65</td>
<td>62 (50.4)</td>
<td>47 (37.9)</td>
<td>58 (47.2)</td>
<td>167 (45.1)</td>
</tr>
<tr>
<td><strong>ALSFRS-R score at screening (mean±SD)</strong></td>
<td>42.1±3.5</td>
<td>41.7±3.8</td>
<td>41.9±3.8</td>
<td>41.9±3.7</td>
</tr>
<tr>
<td><strong>ALSFRS-R at enrolment (mean±SD)</strong></td>
<td>40.1±3.5</td>
<td>39.8±4.0</td>
<td>39.9±4.0</td>
<td>40.0±3.8</td>
</tr>
<tr>
<td><strong>Time lag from symptom onset to diagnosis, months (mean±SD)</strong></td>
<td>19.6±8.1</td>
<td>19.2±8.2</td>
<td>19.7±7.8</td>
<td>19.5±8.0</td>
</tr>
<tr>
<td><strong>%FVC at screening (mean±SD)</strong></td>
<td>97.40±18.22</td>
<td>93.75±17.26</td>
<td>93.99±15.97</td>
<td>95.04±17.21</td>
</tr>
<tr>
<td><strong>%FVC at enrolment (mean±SD)</strong></td>
<td>92.83±20.07</td>
<td>89.98±17.45</td>
<td>89.39±17.55</td>
<td>90.74±18.41</td>
</tr>
<tr>
<td><strong>%FVC change during the observation period (mean±SD)</strong></td>
<td>−4.57±10.63</td>
<td>−3.76±9.36</td>
<td>−4.59±8.77</td>
<td>−4.31±9.60</td>
</tr>
<tr>
<td><strong>Onset type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>30 (24.4)</td>
<td>29 (23.4)</td>
<td>28 (22.8)</td>
<td>87 (23.5)</td>
</tr>
<tr>
<td>UMN</td>
<td>60 (48.8)</td>
<td>62 (50.0)</td>
<td>61 (49.6)</td>
<td>183 (49.5)</td>
</tr>
<tr>
<td>LMN</td>
<td>33 (26.8)</td>
<td>33 (26.6)</td>
<td>34 (27.6)</td>
<td>100 (27.0)</td>
</tr>
<tr>
<td><strong>ALS disease type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic</td>
<td>117 (95.1)</td>
<td>122 (98.4)</td>
<td>118 (95.9)</td>
<td>357 (96.5)</td>
</tr>
<tr>
<td>Familial</td>
<td>6 (4.9)</td>
<td>2 (1.6)</td>
<td>5 (4.1)</td>
<td>13 (3.5)</td>
</tr>
<tr>
<td><strong>Riluzole coadministration during the observation period</strong></td>
<td>110 (89.4)</td>
<td>112 (90.3)</td>
<td>110 (89.4)</td>
<td>332 (89.7)</td>
</tr>
<tr>
<td>Diagnosis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically definite ALS</td>
<td>33 (26.8)</td>
<td>43 (34.7)</td>
<td>49 (39.8)</td>
<td>125 (33.8)</td>
</tr>
<tr>
<td>Clinically probable ALS</td>
<td>62 (50.4)</td>
<td>60 (48.4)</td>
<td>49 (39.8)</td>
<td>171 (46.2)</td>
</tr>
<tr>
<td>Clinically probable, laboratory-supported ALS</td>
<td>28 (22.8)</td>
<td>21 (16.9)</td>
<td>25 (20.3)</td>
<td>74 (20.0)</td>
</tr>
<tr>
<td><strong>ALS severity at enrolment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>14 (11.4)</td>
<td>20 (16.1)</td>
<td>17 (13.8)</td>
<td>51 (13.8)</td>
</tr>
<tr>
<td>Stage II</td>
<td>109 (88.6)</td>
<td>104 (83.9)</td>
<td>106 (86.2)</td>
<td>319 (86.2)</td>
</tr>
<tr>
<td><strong>ALSFRS-R score change during the observation period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1</td>
<td>42 (34.1)</td>
<td>45 (36.3)</td>
<td>42 (34.1)</td>
<td>129 (34.9)</td>
</tr>
<tr>
<td>−2</td>
<td>46 (37.4)</td>
<td>41 (33.1)</td>
<td>45 (36.6)</td>
<td>132 (35.7)</td>
</tr>
<tr>
<td>−3</td>
<td>35 (28.5)</td>
<td>38 (30.6)</td>
<td>36 (29.3)</td>
<td>109 (29.5)</td>
</tr>
</tbody>
</table>

Data were compared among groups using one-way analysis of variance for continuous, χ² test for nominal and Kruskal-Wallis test for ordinal variables. Unless otherwise stated, values represent the number followed by the percentage of participants.

*Diagnoses were made according to the revised El Escorial criteria (Airlie House criteria).

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised ALS Functional Rating Scale; %FVC, per cent-predicted forced vital capacity; LMN, lower motor neuron; UMN, upper motor neuron.

and was considered unrelated to the medication based on the patient’s history. There were no clinically significant changes in the results of laboratory tests, vital signs or ECGs among groups. Statistical details are available on request.

**Classification of evidence**

The research aims of this study were to evaluate the efficacy and safety of long-term ultra-high-dose methylcobalamin (25 mg and 50 mg) in Japanese patients with ALS and the efficacy in patients whose ALS was diagnosed early. Methylcobalamin was not found to be significantly superior to placebo in the whole cohort. However, in patients diagnosed early (≤12 months after symptom onset), this study provides post-hoc class II evidence that ultra-high-dose methylcobalamin prolongs time to death or ventilation support (HR [95% CI]: 0.64 [0.38 to 1.09] for 25 mg group and 0.50 [0.27 to 0.93] for 50 mg group; p=0.01 for placebo vs both methylcobalamin groups combined) and decreased ALSFRS-R scores (p=0.003 for 50 mg and p=0.01 for all methylcobalamin groups) in a dose-responsive manner. The incidence of treatment-related adverse events was similar and low in all groups.

**DISCUSSION**

This long-term study evaluated the efficacy and safety of high-dose methylcobalamin (25 mg and 50 mg administered intramuscularly twice per week) in patients with ALS using the survival (or being fully bound to respirator) as the primary event. Because of the time and expenses incurred, it is becoming more and more difficult to conduct large-scale, long-term studies assessing the survival such as in the present study.

Although the superiority of methylcobalamin over placebo in terms of either the time to primary events or the change in ALSFRS-R score was not confirmed when data from all
participants were analysed, a post-hoc analysis using only the subgroup of patients diagnosed early (diagnosed ≤12 months after symptom onset) demonstrated the efficacy of methylcobalamin. This subgroup suggested dose–response relationships for both survival prolongation and functional measures.

Despite the lack of a statistically significant difference compared with placebo as a whole, deterioration in ALSFRS-R, Manual Muscle Testing (MMT) and Norris scales scores tended to be less pronounced with the higher dose of methylcobalamin. These findings warrant a pivotal phase III clinical trial to be less pronounced with the higher dose of methylcobalamin. This subgroup suggested dose–response relationships after symptom onset.

Alternatively, methylcobalamin may be more efficacious when treatment is started at an early stage of ALS. A recent study observed a primary event (95% CI) was 75.6% (60.1% to 90.1%) for those with a duration of ALS ≤12 months and 51.8% (38.8% to 64.7%) for those >12 months. The median change in the ALSFRS-R scores from baseline to week 182 was −26.5 for those ≤12 months and −21.0 for those >12 months after symptom onset.

Besides those with early diagnosis (ie, rapid disease progression), a similar trend towards poor prognosis regarding time to primary events (or survival) was found in the other two subgroups: being male and having %FVC <90% (online supplementary table e-6). Interestingly, in these three subgroups, methylcobalamin also tended to show a positive influence in the survival and in other endpoints (ALSFRS-R, Norris Scale score and %FVC; online supplementary table e-7). These results could reinforce the efficacy of methylcobalamin in ALS. Provided that findings in favour of methylcobalamin were obtained only in these subgroups and not in the whole cohort, it may be difficult to evaluate the efficacy of a therapeutic drug in patients with slow and variable progression of the disease.

Alternatively, methylcobalamin may be more efficacious when treatment is started at an early stage of ALS. A recent study observed a primary event (95% CI) was 75.6% (60.1% to 90.1%) for those with a duration of ALS ≤12 months and 51.8% (38.8% to 64.7%) for those >12 months. The median change in the ALSFRS-R scores from baseline to week 182 was −26.5 for those ≤12 months and −21.0 for those >12 months after symptom onset.

Table 2 Primary efficacy endpoints analysed in two patient populations

<table>
<thead>
<tr>
<th>Primary efficacy endpoints</th>
<th>Placebo (n=123)</th>
<th>Methylcobalamin</th>
<th>Crude p value (comparison with placebo)</th>
<th>Adjusted p value (comparison with placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to the primary event*, day</td>
<td>25 mg (n=124)</td>
<td>50 mg (n=123)</td>
<td>50 mg</td>
<td>Methylcobalamin</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>880 (678 to 1217)</td>
<td>914 (849 to 1211)</td>
<td>954 (777 to –)</td>
<td>0.33†</td>
</tr>
<tr>
<td>First quartile (25%) (95% CI)</td>
<td>465 (363 to 538)</td>
<td>499 (392 to 610)</td>
<td>503 (377 to 627)</td>
<td>0.15†</td>
</tr>
<tr>
<td>Third quartile (75%) (95% CI)</td>
<td>–‐</td>
<td>–‐</td>
<td>0.88 (0.64 to 1.20)</td>
<td>–‐</td>
</tr>
<tr>
<td>HR vs the placebo group in each active group (95% CI)</td>
<td>–‐</td>
<td>0.83 (0.58 to 1.20)</td>
<td>0.92 (0.65 to 1.32)</td>
<td>0.15†</td>
</tr>
<tr>
<td>Change in ALSFRS-R score</td>
<td>–‐</td>
<td>0.88 (0.64 to 1.20)</td>
<td>–‐</td>
<td></td>
</tr>
<tr>
<td>Patients, n</td>
<td>123</td>
<td>124</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>−24.0 (−42, −1)</td>
<td>−22.0 (−42, 2)</td>
<td>−21.0 (−39, 1)</td>
<td>0.15§</td>
</tr>
<tr>
<td>First quartile (25%)</td>
<td>−30.0</td>
<td>−30.5</td>
<td>−27.0</td>
<td>0.18§</td>
</tr>
<tr>
<td>Third quartile (75%)</td>
<td>−16.0</td>
<td>−12.5</td>
<td>−10.0</td>
<td></td>
</tr>
</tbody>
</table>

* Primary events defined as death for any cause or invasive or non-invasive ventilation support for ≥22 hours due to ALS progression.
†Third quartile of the primary event-free survival was not calculable in any of the groups. P value (comparison with placebo) Analysed using log-rank score.
§Third quartile of the primary event-free survival was not calculable in the 50 mg methylcobalamin group. P value (comparison with placebo) Analysed using Wilcoxon score.
clinical trial of erythropoietin recruiting patients up to 18 months after onset showed a tendency for longer survival and less decrease of ALSFRS-R score up to 6 months.19 Baumann and colleagues20 demonstrated that the half-life of lower motor neurons is approximately 1 year and that these motor neurons decay exponentially in ALS. This means that the number of lower motor neurons is already halved at 1 year after symptom onset. Therefore, in modifying the progression of ALS, a therapeutic agent started late in the progression has only a fraction of the normal lower motor neuron population remaining, with a small number of lower motor neurons sustaining a large number of muscle fibres.

As previously suggested21 the reason so many clinical trials may fail despite the promising results of animal studies is partly due to the late treatment start in humans compared with that in animal models. The El Escorial criteria up to the clinically probable, laboratory-supported level may not be sensitive enough to detect patients with ALS in the early stage of the disease for participation in clinical trials, in contrast to the detection criteria used in animal studies.

In clinical settings, the average delay from symptom onset to an ALS diagnosis is approximately 1 year, and a delay of ≤12 months accounts for about 40% of patients.21–23 The newly developed Awaji criteria,24 incorporated into the El Escorial criteria, may shorten the delay to 9 months.25–28 In this study, methylcobalamin showed prominent prolongation of survival with slower functional decline in patients diagnosed early (≤12 months after symptom onset). Currently, approximately half of the ALS population could benefit from methylcobalamin treatment using the revised El Escorial diagnostic criteria; however, if the use of the Awaji criteria becomes the standard practice, most patients could benefit from this therapy, if the promise is fulfilled in the currently ongoing JETALS study, which uses the Awaji criteria for entry for the first time. The inconvenience of intramuscular injections may be overcome by allowing injections by patients or their caregivers, which is currently employed in the JETALS study.

Further limitations of this trial should be noted. First, the strict criteria for study inclusion may have excluded some patients with ALS, which has heterogeneous pathogeneses. Second, although post-hoc analysis identified only one subgroup of patients, additional factors may influence the efficacy and safety profile of methylcobalamin. Third, we did not examine higher doses (>50 mg) for dose finding, and it is possible that these mega-doses might have even better outcome. These potential factors may warrant future analyses in other study cohorts such as JETALS.

In conclusion, ultra-high-dose methylcobalamin was not found to be significantly superior to placebo. However, ultra-high-dose methylcobalamin therapy may improve the prognosis of patients with ALS if administered early in the disease course. Therapeutic agents that failed in the previous clinical trials could be reanalysed for potential efficacy in ALS, taking into account the duration of the disease at the start of therapy. Criteria enabling earlier diagnosis and a change in the physician’s attitude towards offering an early diagnosis and treatment should yield better future outcomes for the patients than ever.

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Acknowledgements We thank all patients for their participation and the staff site for their contributions. Contributors (trial conduct supervision by site): Ichiro Vabe (Hokkaido University Hospital), Jun Kawamata (Sapporo Medical University Hospital), Hiroto Takada (National Hospital Organization Aomori Hospital), Keiji Chida (National Hospital Organization Iwate Hospital), Masashi Aoki (Tohoku University Hospital), Hiroaki Itô (National Hospital Organization Miyagi Hospital), Masashiro Sugawara (Akita University Hospital), Munetoshi Tobita (National Hospital Organization Yonezawa Hospital), Yoshihiro Sugii (Fukushima Medical University Hospital), Mitsuya Morita (Jichi Medical University Hospital), Yukio Fujita (Gunma University Hospital), Yuichi Maruki (Saitama Neuropsychiatric Institute), Katsuhisa Ogata (National Hospital Organization Higashi Saitama Hospital), Kimihito Ari (National Hospital Organization Chiba-East Hospital), Hidehito Mizusawa (Tokyo Medical and Dental University Hospital), Masashi Takano (Juntendo University Hospital), Yasuo Iwatski (Toho University Otori Medical Center), Takashi Sakamoto (National Center Hospital, National Center of Neurology and Psychiatry), Mieko Ogiio (The Kitasato Institute, Kitasato University East Hospital), Kazuko Hasegawa (National Hospital Organization Sagamihara Hospital), Ichiro Imakuku (Japan Labour Health and Welfare Organization, Yokohama Rosai Hospital), Kazuhiro Muramatsu (Saiseikai Yokohama-shi Tobu Hospital), Ryoko Kikoku (National Hospital Organization Nishi-Niigata Chuo Hospital), Yousuke Yonemochi (National Hospital Organization Niigata Hospital), Kyounobu Komai (National Hospital Organization Iou Hospital), Hiyori Yakiwazawa (Nagano Red Cross Hospital), Koichi Mizoguchi (National Hospital Organization, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders), Tatsuyoshi Uchiyama (Seirei Social Welfare Community, Seirei Hamamatsu General Hospital), Naoki Atsuta (Nagoya University Hospital), Kazuya Nokura (Fujita Health University), Kazutoshi Kobayashi (Kansai University Hospital), Kengo Maeda (Shiga University of Medical Science Hospital), Hideyuki Sawada (National Hospital Organization Utano Hospital), Toshihiko Mizuno (University Hospital Kyoto Prefectural, University of Medicine), Harutoshi Fujimura (National Hospital Organization Toneyama Hospital), Kenya Murata (Wakayama Medical University Hospital), Yuetso Ihara (National Hospital Organization Minami-Osakayama Medical Center), Kouichi Noda (National Hospital Organization Higashishinshu Medical Center), Masanori Hijji (Mifukai Vihara Hananotsu Hospital), Chisuga Watanabe (National Hospital Organization Hiroshima-Nishi Medical Center), Takeo Yoshimura (Shakaihoken Shinmonoski Koheisi Hospital), Hiromasa Fukuba (National Hospital Organization Yokai Medical Center), Ryujirou Kajj (Tokushima University Hospital), Shuji Hashiguchi (National Hospital Organization Tokushu Hospital), Masahiro Nomoto (Elme University Hospital), Yasushi Osaki (Kochi Medical School Hospital), Hiyori Nakazawa (Nankoku Hospital), Hirotoki Kikuchi (Murakami Karinoh Hospital), Tomoaki Yuki (Hospital of University of Occupational and Environmental Health, Japan), Tomoko Narita (National Hospital Organization Nagasaki Kawanata Medical Center) and Masahito Suhear (National Hospital Organization Okinawa Hospital). Draft manuscript editing was provided by Clinical Study Support (Nagoya, Japan) under contract with Eisai. Statistical analysis was conducted by Yasuo Ohashi, PhD, Chuo University, Department of Integrated Science and Engineering for Sustainable Society, and Takao Takase, MSc, Eisai.

Contributions RK designed the study, interpreted the data and drafted the manuscript. TI designed the study. VJ designed the study. KO designed the study. MN designed the study. YO designed the study and performed the statistical analysis. TT designed the study, performed the statistical analysis, interpreted the data and drafted the manuscript. HS designed the study, interpreted the data and drafted the manuscript. KT designed the study and interpreted the data. SK designed the study and interpreted the data. Funding This study was funded by Eisai. Competing interests RK received grants from Eisai during the conduct of the study and has a patent on the Method of treating amyotrophic lateral sclerosis (US 20130344081 A1 licensed). TI received grants from Eisai during the conduct of the study. VJ reports no disclosures. KO reports no disclosures. MN reports no disclosures. YO received personal fees from Statcom, Sanofi, Eisai, Chugai, Taiho, Shionogi, and Kowa, and non-financial support from Yakult Honsha and Takeda outside the submitted work. TT is employed by Eisai. HS is employed by Eisai. KT received grants from Eisai during the conduct of the study. SK received grants from Eisai during the conduct of the study. Patient consent for publication Not required. Ethics approval This study is conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each centre. All eligible patients provided written informed consent. Provenance and peer review Not commissioned; externally peer reviewed. Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

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