Table e-1. Secondary efficacy endpoints at week 182 and change from baseline to week 182

			Methylcobalamin				*P* value	
	Placebo		25 mg		50 mg		(Comparison with placebo)	
	n	Median (min, max)	n	Median (min, max)	n	Median (min, max)	50 mg	Methylcobalamin
%FVC								
Baseline	123	91.70 (60.8, 160.3)	124	91.75 (60.2, 127.1)	123	89.20 (60.5, 139.8)		
Week 182	122	35.80 (0.0, 114.1)	124	42.25 (1.9, 119.4)	122	39.15 (2.2, 150.3)		
Change	122	−48.90 (−112.5, 5.7)	124	−40.60 (−113.3, 8.8)	122	−43.55 (−105.5, 19.2)	0.12	0.08
MMT								
Baseline	123	44.0 (21, 55)	124	45.0 (22, 55)	123	43.0 (22, 55)		
Week 182	123	21.0 (0, 55)	124	24.0 (1, 55)	122	24.0 (0, 55)		
Change	123	−22.0 (−50, 3)	124	−19.0 (−43, 10)	122	−17.0 (−45, 6)	0.12	0.03
Grip strength (right hand), kg								
Baseline	123	13.0 (0, 45)	124	15.0 (0, 43)	123	13.0 (0, 48)		
Week 182	123	0.0 (0, 34)	124	0.0 (0, 35)	122	0.0 (0, 29)		
Change	123	−9.0 (−44, 2)	124	−9.0 (−34, 6)	122	−9.0 (−37, 8)	0.28	0.11
Grip strength (left hand), kg								
Baseline	123	13.0 (0, 46)	124	14.0 (0, 45)	123	12.0 (0, 44)		
Week 182	123	0.0 (0, 33)	124	0.0 (0, 44)	122	0.0 (0, 29)		
Change	123	−9.0 (−41, 5)	124	−9.0 (−41, 3)	122	−8.0 (−44, 7)	0.18	0.03
Norris scale score								
Baseline	123	85.0 (44, 101)	124	84.0 (39, 102)	123	84.0 (40, 101)		
Week 182	123	32.0 (0, 102)	124	33.0 (0, 101)	122	35.5 (0, 102)		

Change	123	−53.0 (−92, 1)	124	−50.0 (−92, 0)	122	−46.0 (−87, 1)	0.10	0.03
ALSAQ-40 score								
Baseline	121	99.0 (54, 176)	120	97.0 (45, 180)	121	100.0 (42, 179)		
Week 182	122	170.0 (40, 200)	124	158.0 (47, 200)	121	158.0 (49, 200)		
Change	120	63.0 (−26, 128)	120	53.5 (−47, 141)	119	55.0 (−14, 112)	0.58	0.63

%FVC denotes percent-predicted forced vital capacity, MMT denotes manual muscle testing, and ALSAQ-40 denotes ALS assessment questionnaire-40.

Table e-2. Influence of interval from symptom onset to diagnosis at study enrollment on time to primary events[a]

Interval from symptom onset to diagnosis (month)	Number of patients			Hazard ratio vs Placebo (95% CI)			*P* value (Comparison with placebo)	
	Placebo	25 mg	50 mg	25 mg	50 mg	Total	50 mg	Methylcobalamin
≤7	13	13	10	0.26 (0.08, 0.80)	0.23 (0.06, 0.89)	0.24 (0.09, 0.69)	0.007	0.001
≤8	20	21	13	0.60 (0.25, 1.44)	0.73 (0.27, 1.96)	0.66 (0.30, 1.44)	0.218	0.132
≤9	28	28	22	0.56 (0.27, 1.16)	0.43 (0.19, 0.96)	0.49 (0.26, 0.93)	0.016	0.014
≤10	34	35	31	0.63 (0.33, 1.21)	0.48 (0.24, 0.99)	0.55 (0.31, 0.98)	0.020	0.022
≤11	43	45	37	0.56 (0.31, 1.01)	0.55 (0.29, 1.04)	0.55 (0.33, 0.93)	0.025	0.011
≤12	48	54	42	0.64 (0.38, 1.09)	0.50 (0.27, 0.93)	0.57 (0.35, 0.92)	0.010	0.011
≤13	51	61	49	0.73 (0.44, 1.21)	0.59 (0.33, 1.05)	0.66 (0.42, 1.04)	0.033	0.040
≤14	55	62	57	0.70 (0.43, 1.15)	0.56 (0.33, 0.95)	0.62 (0.40, 0.97)	0.014	0.017
≤15	60	67	62	0.76 (0.47, 1.25)	0.66 (0.39, 1.11)	0.71 (0.46, 1.09)	0.055	0.060
≤16	63	71	65	0.87 (0.54, 1.40)	0.72 (0.43, 1.18)	0.79 (0.52, 1.20)	0.095	0.140
≤17	69	76	67	0.86 (0.55, 1.35)	0.73 (0.45, 1.18)	0.79 (0.53, 1.18)	0.096	0.129
≤18	76	78	72	0.97 (0.63, 1.50)	0.84 (0.53, 1.33)	0.90 (0.61, 1.32)	0.223	0.302
≤19	77	81	80	0.92 (0.60, 1.42)	0.81 (0.52, 1.26)	0.86 (0.59, 1.26)	0.168	0.218
≤20	83	86	85	0.85 (0.56, 1.29)	0.79 (0.52, 1.20)	0.82 (0.57, 1.18)	0.133	0.140
≤21	86	89	93	0.90 (0.60, 1.35)	0.82 (0.54, 1.24)	0.86 (0.60, 1.22)	0.169	0.196
≤22	89	92	94	0.86 (0.58, 1.29)	0.81 (0.54, 1.21)	0.84 (0.59, 1.18)	0.150	0.153
≤23	95	94	97	0.87 (0.59, 1.29)	0.86 (0.58, 1.28)	0.87 (0.62, 1.22)	0.225	0.203
≤24	101	99	100	0.89 (0.61, 1.31)	0.84 (0.57, 1.24)	0.87 (0.62, 1.21)	0.187	0.195
FAS	123	124	123	0.83 (0.58, 1.20)	0.92 (0.65, 1.32)	0.88 (0.64, 1.20)	0.330	0.204

[a] Primary events defined as death for any cause or invasive or non-invasive ventilation support for ≥22 hours due to ALS progression. Inter-group differences analyzed using log-rank scores.

Table e-3. Influence of interval from symptom onset to diagnosis at study enrollment on ALSFRS-R

Interval from symptom onset to diagnosis (month)	Placebo		Methylcobalamin 25 mg		Methylcobalamin 50 mg		*P* value (Comparison with placebo)	
	n	Median (min, max)	n	Median (min, max)	n	Median (min, max)	50 mg	Methylcobalamin
≤7	13	−26.0 (−40, −4)	13	−27.0 (−38, −12)	10	−24.5 (−34, 1)	0.002	0.004
≤8	20	−25.5 (−40, −4)	21	−27.0 (−38, 0)	13	−26.0 (−38, 1)	0.073	0.049
≤9	28	−26.5 (−40, −3)	28	−27.5 (−40, 0)	21	−23.0 (−38, 1)	0.075	0.065
≤10	34	−26.5 (−40, −3)	35	−28.0 (−40, 0)	30	−23.0 (−38, 1)	0.019	0.036
≤11	43	−27.0 (−40, −3)	45	−27.0 (−40, 0)	37	−21.5 (−38, 1)	0.009	0.021
≤12	48	−26.5 (−40, −3)	54	−26.5 (−40, 0)	41	−22.0 (−38, 1)	0.003	0.013
≤13	51	−27.0 (−42, −3)	61	−26.0 (−40, 0)	48	−22.0 (−39, 1)	0.009	0.025
≤14	55	−26.0 (−42, −3)	62	−25.5 (−40, 0)	56	−23.0 (−39, 1)	0.018	0.037
≤15	60	−26.0 (−42, 0)	67	−25.0 (−40, 0)	61	−23.0 (−39, 1)	0.043	0.079
≤16	63	−25.0 (−42, 0)	71	−24.0 (−40, 0)	64	−23.0 (−39, 1)	0.051	0.125
≤17	69	−25.0 (−42, 0)	76	−24.0 (−42, 0)	66	−22.5 (−39, 1)	0.039	0.118
≤18	76	−25.0 (−42, 0)	78	−24.0 (−42, 0)	71	−22.0 (−39, 1)	0.079	0.204
≤19	77	−25.0 (−42, 0)	81	−24.0 (−42, 0)	79	−22.0 (−39, 1)	0.046	0.118
≤20	83	−25.0 (−42, 0)	86	−24.0 (−42, 0)	84	−22.0 (−39, 1)	0.031	0.086
≤21	86	−25.0 (−42, 0)	89	−24.0 (−42, 0)	92	−22.0 (−39, 1)	0.023	0.076
≤22	89	−25.0 (−42, 0)	92	−23.5 (−42, 0)	93	−22.0 (−39, 1)	0.011	0.029
≤23	95	−25.0 (−42, 0)	94	−23.5 (−42, 0)	96	−22.0 (−39, 1)	0.015	0.031
≤24	101	−25.0 (−42, 0)	99	−23.0 (−42, 0)	99	−22.0 (−39, 1)	0.024	0.049

FAS	123	−24.0 (−42, 1)	124	−22.0 (−42, 2)	122	−21.0 (−39, 1)	0.150	0.087

ALSFRS-R denotes revised ALS functional rating scale

Inter-group differences analyzed using Wilcoxon scores.

Table e-4. Secondary efficacy endpoints at week 182 and change from baseline to week 182 in the subgroup of patients diagnosed early (diagnosed ≤12 months after symptom onset)

			Methylcobalamin				*P* value	
	Placebo		25 mg		50 mg		(Comparison with placebo)	
	n	Median (min, max)	n	Median (min, max)	n	Median (min, max)	50 mg	Methylcobalamin
%FVC								
Baseline	48	89.90 (60.8, 160.3)	54	93.55 (60.2, 127.1)	42	92.05 (63.2, 116.5)		
Week 182	48	35.05 (0.0, 90.7)	54	41.20 (1.9, 119.4)	41	44.80 (10.7, 107.3)		
Change	48	−50.65 (−99.7, −1.9)	54	−49.15 (−113.3, 8.8)	41	−39.50 (−105.5, 1.9)	<0.001	0.004
MMT								
Baseline	48	43.5 (22, 55)	54	45.5 (30, 55)	42	45.0 (29, 55)		
Week 182	48	20.0 (0, 48)	54	23.0 (1, 49)	41	27.0 (1, 55)		
Change	48	−24.0 (−45, −1)	54	−22.0 (−43, 1)	41	−17.0 (−43, 2)	0.04	0.05
Grip strength (right hand), kg								
Baseline	48	14.5 (0, 45)	54	14.5 (0, 43)	42	12.5 (0, 48)		
Week 182	48	0.0 (0, 27)	54	0.0 (0, 29)	41	0.0 (0, 26)		
Change	48	−11.5 (−44, 0)	54	−10.0 (−28, 2)	41	−11.0 (−34, 7)	0.11	0.07
Grip strength (left hand), kg								
Baseline	48	12.5 (0, 46)	54	14.0 (0, 41)	42	14.0 (0, 44)		
Week 182	48	0.0 (0, 30)	54	0.0 (0, 44)	41	0.0 (0, 29)		
Change	48	−11.0 (−34, 0)	54	−10.5 (−41, 3)	41	−10.0 (−44, 7)	0.08	0.04
Norris scale score								
Baseline	48	86.5 (55, 100)	54	86.0 (61, 100)	42	89.0 (61, 101)		

Week 182	48	21.5 (0, 92)	54	28.5 (0, 98)	41	41.0 (0, 102)		
Change	48	−58.0 (−92, 0)	54	−56.5 (−91, −1)	41	−47.0 (−87, 1)	0.005	0.008
ALSAQ-40 score								
Baseline	47	95.0 (59, 176)	51	94.0 (45, 180)	42	94.5 (42, 131)		
Week 182	47	177.0 (85, 200)	54	168.5 (55, 200)	40	153.0 (49, 200)		
Change	46	66.0 (−1, 128)	51	66.0 (−47, 141)	40	49.5 (−14, 106)	0.54	0.35

%FVC denotes percent-predicted forced vital capacity, MMT denotes manual muscle testing, and ALSAQ-40 denotes ALS assessment questionnaire-40.

Table e-5. Prognostic factors selected by the Cox proportional hazards model with backward elimination for the placebo group

Covariates		Full Model				Final Model			
Variables	Category	Parameter Estimate	Standard Error	*P* value	Hazard ratio	Parameter Estimate	Standard Error	*P* value	Hazard ratio
Interval from symptom onset to diagnosis	≤12 month / >12 month	−1.492	0.392	<0.001	0.225	−0.861	0.265	0.001	0.423
Serum triglyceride	<130 mg/dL / ≥130 mg/dL	−0.226	0.297	0.446	0.798				
Age	≥ 65 /< 65	−0.287	0.308	0.352	0.751				
Gender	Female / Male	1.380	0.376	<0.001	3.973	0.589	0.272	0.030	1.802
Site of onset	Bulbar onset / Others	−0.323	0.334	0.333	0.724				
Revised El Escorial criteria (Airlie House criteria) at enrollment	Clinically definite ALS / Others	0.061	0.343	0.858	1.063				
ALSFRS-R total score at end of observation period	≤37 / 38 − 42	−0.892	0.405	0.027	0.410				
	≤37 / ≥43	−1.324	0.537	0.013	0.266				
Decline of ALSFRS-R total score during observation period	−3 / −2	−0.581	0.359	0.105	0.559				
	−3 / −1	−0.222	0.354	0.530	0.801				
Progression rate of ALSFRS-R	<0.36 / ≥0.36	−0.284	0.422	0.501	0.753				
%FVC (end of observation period)	<90%/ ≥90%	−1.137	0.320	<0.001	0.321	−1.402	0.278	<0.001	0.246
Serum creatinine (end of observation period)	<0.6 / ≥0.6	−0.939	0.376	0.012	0.391				

Serum total cholesterol (end of observation period)	<200 mg/dL / ≥200 mg/dL	0.257	0.289	0.374	1.293				
Riluzole	No / Yes	−0.879	0.426	0.039	0.415	−1.016	0.398	0.010	0.362

P values obtained from the Wald Chi-square test statistics.

A significance level to stay covariates from all candidate variables in the final model set at 0.05.

Table e-6. Time to primary events[a] in the subgroup of patients with selected prognostic factors

	Hazard ratio vs Placebo (95% CI)			*P* value (Comparison with placebo)		
	25 mg	50 mg	Total	25 mg	50 mg	Total
≤12 months[b]	0.64 (0.38, 1.09)	0.50 (0.27, 0.93)	0.57 (0.35, 0.92)	0.052	0.010	0.011
Male	0.77 (0.49, 1.22)	0.77 (0.49, 1.22)	0.77 (0.52, 1.14)	0.130	0.132	0.096
%FVC <90%	0.76 (0.48, 1.21)	0.76 (0.48, 1.22)	0.76 (0.51, 1.14)	0.126	0.126	0.090

[a] Primary events defined as death for any cause or invasive or non-invasive ventilation support for ≥22 hours due to ALS progression. Inter-group differences analyzed using log-rank scores.

[b] Patients diagnosed ≤12 months after symptom onset

Table e-7. Efficacy endpoints at week 182 and change from baseline to week 182 in the subgroup of patients with selected prognostic factors

	Placebo		Methylcobalamin 25 mg		Methylcobalamin 50 mg		*P* value (Comparison with placebo)	
	n	Median (min, max)	n	Median (min, max)	n	Median (min, max)	50 mg	Methyl-cobalamin
Change in total ALSFRS−R								
≤12 months[a]	48	−26.5 (−40, −3)	54	−26.5 (−40, 0)	41	−22.0 (−38, 1)	0.003	0.013
Male	71	−22.0 (−42, 1)	81	−22.0 (−42, 2)	71	−18.0 (−39, 1)	0.095	0.074
%FVC<90%	57	−25.0 (−38, 0)	60	−22.5 (−40, −3)	62	−19.0 (−39, 1)	0.020	0.022
Change in ALSFRS−R, Bulbar function								
≤12 months[a]	48	−6.0 (−12, 0)	54	−4.0 (−12, 0)	41	−4.0 (−8, 0)	0.003	0.007
Male	71	−4.0 (−12, 2)	81	−4.0 (−12, 0)	71	−3.0 (−10, 1)	0.060	0.048
%FVC<90%	57	−5.0 (−11, 0)	60	−4.0 (−11, 0)	62	−3.0 (−10, 0)	0.028	0.019
Change in ALSFRS−R, Motor function								
≤12 months[a]	48	−15.0 (−21, −3)	54	−14.0 (−20, 0)	41	−11.0 (−22, 1)	0.038	0.044
Male	71	−13.0 (−24, 1)	81	−13.0 (−21, 1)	71	−10.0 (−22, 0)	0.163	0.112
%FVC<90%	57	−13.0 (−21, 0)	60	−12.0 (−22, 0)	62	−9.0 (−20, 0)	0.038	0.031
Change in ALSFRS−R, Respiratory function								
≤12 months[a]	48	−6.0 (−12, 0)	54	−7.0 (−12, 0)	41	−2.0 (−12, 0)	0.004	0.020
Male	71	−5.0 (−12, 0)	81	−4.0 (−12, 1)	71	−1.0 (−12, 1)	0.105	0.081
%FVC<90%	57	−7.0 (−12, 0)	60	−7.0 (−12, 0)	63	−4.0 (−12, 1)	0.029	0.033
Change in total Norris scale								
≤12 months[a]	48	−58.0 (−92, 0)	54	−56.5 (−91, −1)	41	−47.0 (−87, 1)	0.005	0.008
Male	71	−52.0 (−92, 1)	81	−50.0 (−92, 0)	71	−43.0 (−86, 1)	0.107	0.054
%FVC<90%	57	−52.0 (−86, 0)	60	−50.5 (−77, −12)	62	−40.5 (−87, −4)	0.033	0.017
Change in Norris scale, Limb								
≤12 months[a]	48	−38.5 (−59, 0)	54	−41.0 (−55, 0)	41	−33.0 (−60, 1)	0.038	0.052
Male	71	−36.0 (−62, 1)	81	−35.0 (−58, 0)	71	−28.0 (−60, 1)	0.204	0.121
%FVC<90%	57	−34.0 (−58, 0)	60	−33.5 (−61, 0)	62	−25.0 (−58, 0)	0.070	0.051
Change in Norris scale, Bulbar								
≤12 months[a]	48	−21.0 (−39, 0)	54	−16.0 (−38, 0)	41	−12.0 (−34, 0)	0.002	0.002
Male	71	−14.0 (−39, 1)	81	−12.0 (−34, 0)	71	−10.0 (−35, 0)	0.065	0.027
%FVC<90%	57	−18.0 (−39, 0)	60	−13.0 (−34, −1)	62	−11.5 (−35, 0)	0.029	0.010
Change in %FVC								
≤12 months[a]	48	−50.7 (−99.7,−1.9)	54	−49.2 (−113.3, 8.8)	41	−39.5 (−105.5, 1.9)	<0.001	0.004

Male	70	−46.1 (−104.7, 5.7)	81	−38.5 (−88.2, 8.8)	71	−39.30 (−105.5, 19.2)	0.038	0.035
%FVC<90%	56	−41.4 (−87.2, 4.2)	60	−38.2 (−81.4, 6.0)	62	−36.9 (−70.4, 19.2)	0.029	0.038

ALSFRS-R denotes revised ALS functional rating scale.

%FVC denotes percent-predicted forced vital capacity.

Inter-group differences analyzed using Wilcoxon scores.

[a] Patients diagnosed ≤12 months after symptom onset