Effect of High-Caloric Nutrition on Survival in Amyotrophic Lateral Sclerosis

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Objective: Weight loss has been identified as a negative prognostic factor in amyotrophic lateral sclerosis, but there is no evidence regarding whether a high-caloric diet increases survival. Therefore, we sought to evaluate the efficacy of a high-caloric fatty diet (HCFD) for increasing survival.

Methods: A 1:1 randomized, placebo-controlled, parallel-group, double-blinded trial (LIPCAL-ALS study) was conducted between February 2015 and September 2018. Patients were followed up at 3, 6, 9, 12, 15, and 18 months after randomization. The study was performed at 12 sites of the clinical and scientific network of German motor neuron disease centers (ALS/MND-NET). Eligible patients were randomly assigned (1:1) to receive either HCFD (405kcal/day, 100% fat) or placebo in addition to riluzole (100mg/day). The primary endpoint was survival time, defined as time to death or time to study cutoff date.

Results: Two hundred one patients (80 female, 121 male, age = 62.4 ± 10.8 years) were included. The confirmatory analysis of the primary outcome survival showed a survival probability of 0.39 (95% confidence interval [CI] = 0.27–0.51) in the placebo group and 0.37 (95% CI = 0.25–0.49) in the HCFD group, both after 28 months (point in time of the last event). The hazard ratio was 0.97, 1-sided 97.5% CI = $-\infty$ to 1.44, $p = 0.44$.

Interpretation: The results provide no evidence for a life-prolonging effect of HCFD for the whole amyotrophic lateral sclerosis population. However, post hoc analysis revealed a significant survival benefit for the subgroup of fast-progressing patients.

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Amyotrophic lateral sclerosis (ALS) is the most frequent adult onset motor neuron disease, simultaneously affecting upper, cortical, and lower brainstem and spinal cord motor neurons, leading to death through respiratory insufficiency within about 3 years after disease onset.[1–3]

Epidemiological evidence suggests that ALS patients suffer from catabolism[4] and begin to lose weight > 10 years before the onset of motor symptoms.[5,6] Furthermore, increased risk of ALS is associated with lower body mass index[7,8] as well as with abnormal levels of circulating metabolic hormones.[9,10] Moreover, weight loss[11–14] and metabolic status indirectly assessed by circulating lipids[15] or body fat distribution[16] are strong predictors of survival. Weight loss is correlated with structural defects in the hypothalamus, the integration center of energy metabolism,[17–20] suggesting the importance of abnormalities driven by the central nervous system. Catabolism may also result from the combination of dysphagia and intrinsic hypermetabolism, as shown in ALS patients[21–23] as well as a mouse model of ALS.[24]

It has been shown that high-caloric nutrition can stabilize body weight.[25] Targeting weight loss in ALS may be therapeutically useful, because increasing energy content of the diet increased survival in ALS mouse models[24] and showed efficacy in humans in a pilot clinical trial in gastrostomized ALS patients[26] as well as in a longitudinal register of percutaneous endoscopic gastrostomy (PEG)-implanted patients.[27]

However, direct evidence for a therapeutic effect of increased calorie intake is missing, and it is not known whether patients without bulbar involvement and without weight loss might benefit as well. Furthermore, it is not known which kind of high-caloric supplement should be used, that is, whether a high-fat, high-carbohydrate, or high-protein nutrition should be preferred. In this context, several studies suggest that high cholesterol[15] and triglyceride levels[28] are possibly associated with a better prognosis.

Therefore, we performed a prospective, double-blind, randomized, placebo-controlled clinical trial to investigate the efficacy and tolerability of a high-caloric fatty diet (HCFD) in ALS.

Patients and Methods

Study Design and Participants

This study was a prospective, randomized, double-blind, parallel-group, placebo-controlled trial of HCFD as an add-on therapy to standard treatment (riluzole) in patients with ALS. It was conducted at 12 sites of the clinical and scientific network of German motor neuron disease centers (ALS/MND-NET) and was done in accordance with the Declaration of Helsinki, International Conference on Harmonization Guideline for Good Clinical Practice, and the applicable local regulations. The independent ethics committee of Ulm University, Germany approved the study protocol (approval number 300/14), and independent ethics committees of each participating study site followed this vote and approved the study. For 3-monthly review of safety results, an independent data safety and monitoring board was established before the start of the study. The trial is registered with ClinicalTrials.gov, number NCT02306590.

Patients with possible, probable (clinically or laboratory-supported), or definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria were considered for enrollment into the study.[29] Included patients had a disease duration of >6 months and < 3 years, with disease onset defined as date of first muscle weakness, excluding fasciculation and cramps. They reached a best-sitting slow vital capacity (SVC) of at least 50% and were willing to complete a diet questionnaire throughout participation in the study. All included patients had been treated with 100mg riluzole daily for at least 4 weeks prior to inclusion. A complete list of the inclusion and exclusion criteria is provided in the Supplementary Material.

Randomization and Masking

At visit 1 (baseline), eligible patients were enrolled into the study. Each eligible patient was randomly assigned (1:1) to 1 of the 2 treatment groups, and received the next consecutive randomization number according to their stratum.

The randomization list was generated by an independent person at the Institute of Epidemiology and Medical Biometry, University of Ulm, Germany, by use of a validated system, which involves a pseudorandom number generator to ensure that the resulting treatment sequence will be both reproducible and nonpredictable. The randomization list was kept safe at the Institute of Epidemiology and Medical Biometry, and the independent person was not involved in the statistical analysis.

The randomization was performed centrally by the Ulm University Hospital pharmacy (drug depot) and stratified according to bulbar or spinal onset of the disease and body mass index (BMI) status. Regarding BMI, patients were assigned to "low BMI" (≤21.75kg/m^2) versus "high BMI" (>21.75kg/m^2). The cutoff point of BMI strata was the middle of normal weight range according to BMI classification.[30]

The trial was double-blinded; patients and site personnel were masked to treatment allocation. The dietary supplement (Calogen; Nutricia, Erlangen Germany) is commercially available; placebo solution was manufactured by the Ulm University Hospital pharmacy. The composition of both supplements (identical look and consistency) is listed in the Supplementary Material. Blinding, packaging, and

labeling were performed by the Ulm University Hospital pharmacy according to the randomization list. A central unblinding procedure was established.

Procedures

Patients allocated to the intervention group (verum) received 30ml of HCFD 3 times per day (equivalent to an additional fat intake of 45g and an additional calorie intake of 405kcal per day). Patients allocated to the placebo group received 30ml of the matching placebo solution 3 times per day (equivalent to an additional fat intake of 0.1g and an additional calorie intake of 8kcal per day).

Patients were instructed to take the intervention in addition to their normal food intake and to otherwise maintain their usual eating habits. Daily additional food intake was controlled by a standardized nutrition and appetite score (Council of Nutrition Appetite Questionnaire [CNAQ]) as well as a nutrition questionnaire comprising questions about nutrition habits, such as number of meals per day and composition of meals. By these measures, we aimed to control a potential bias caused by a change of eating habits (ie, verum patients reducing their usual food intake due to decreased appetite caused by the intervention).

Clinical and physical examinations (outcome measures), blood sampling, and study compliance were recorded at on-site visits (6, 12, and 18 months after baseline [V1]). Body weight and functional status, including noninvasive ventilation and Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R), were additionally recorded at 3, 9, and 15 months after baseline through telephone contacts. Long-term survival status of all study participants was collected at the completion of the study (last patient's last visit plus 14 days safety follow-up).

Data were recorded and initially processed using the clinical data management system MACRO (InferMed, London, UK). MACRO supports the requirements of International Conference on Harmonization-good clinical practice (ICH-GCP), Code of Federal Regulations Title 21 (21 CFR) Part 11, and the EU Clinical Trials Directive. Data were entered by each trial site directly into the MACRO database via protected Internet connection.

Outcomes

The primary endpoint was survival time, that is, the time from randomization until death or the end of the trial (completion of the whole study). Secondary efficacy outcomes were change (ie, difference from baseline) of total score on the ALSFRS-R, change of SVC (effect on vital capacity), and change in individual quality of life using the Schedule for the Evaluation of Individual Quality of Life (SEIQoL) score, time to tracheostomy or death (combined), change of BMI, and change of CNAQ. Safety endpoints included the terms and frequency of reported adverse events and serious adverse events as well as safety laboratory parameters (clinical chemistry and hematology) and vital signs.

Statistical Analysis

We calculated the sample size on the basis of a comparison of 2 survival curves with the 1-sided log-rank test. We made the following assumptions: type I error = 0.025,

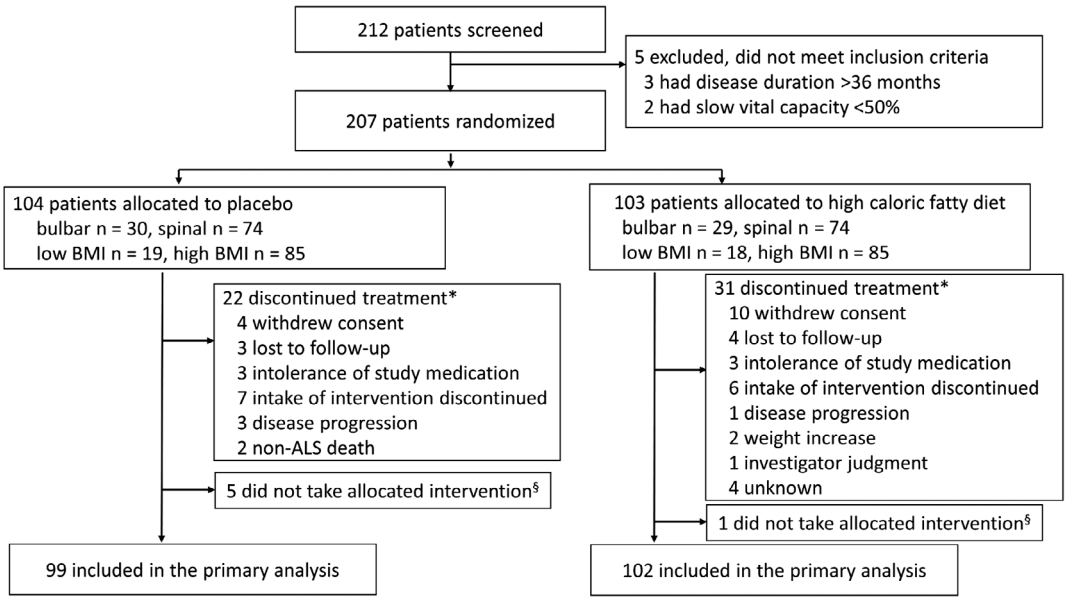


FIGURE 1: Trial profile, full analysis set. *Survival time for discontinued study participants was censored at the time of discontinuation and used in the primary analysis. §One patient in the high-caloric fatty diet group and 5 patients in the placebo group did not take the allocated intervention and were excluded from the primary analysis. ALS = amyotrophic lateral sclerosis; BMI = body mass index.

power = 0.80, recruiting time = 9 months, length of follow-up = 18 months, 18 months survival rate of 70% in the placebo group, and 18 months survival rate of 85% in the HCFD group, which was regarded as a clinically relevant difference (hazard ratio [HR] = 0.46). Under the assumption of equal numbers of patients in each group, this scenario required 200 patients (100 per group) and 54 events in total.

TABLE 1. Patient Characteristics at Baseline (Full Analysis Set Population)

Characteristic	High-Caloric Fatty Diet, n = 102	Placebo, n = 99	Total, n = 201
Age, yr	62.4 ± 11.0	62.4 ± 10.6	62.4 ± 10.8
Sex			
Female	41 (40.2%)	39 (39.4%)	80 (39.8%)
Male	61 (59.8%)	60 (60.6%)	121 (60.2%)
Weight, kg	73.4 ± 12.7	74.4 ± 13.6	73.9 ± 13.1
BMI, kg/m^2	25.0 ± 4.2	24.7 ± 3.5	24.9 ± 3.9
BMI			
≤21.75kg/m^2	18 (17.7%)	19 (19.2%)	37 (18.4%)
>21.75kg/m^2	84 (82.3%)	80 (80.8%)	164 (81.6%)
Onset			
Bulbar	29 (28.4%)	29 (29.3%)	58 (28.9%)
Spinal	73 (71.6%)	70 (70.7%)	143 (71.1%)
Duration of disease, mo[a]	15.5 [9.6–23.2]	15.4 [9.9–25.3]	15.4 [9.8–24.3]
Time since diagnosis, mo[b]	6.0 [2.6–11.4]	5.2 [2.7–9.6]	5.8 [2.6–11.3]
Certainty of diagnosis			
Definite	19 (18.6%)	16 (16.2%)	35 (17.4%)
Probable	41 (40.2%)	39 (39.4%)	80 (39.8%)
Laboratory-supported probable	31 (30.4%)	29 (29.3%)	60 (29.9%)
Possible	8 (7.8%)	8 (8.1%)	16 (8.0%)
ALS variants	3 (2.9%)	7 (7.1%)	10 (5.0%)
Progression rate[c]			
Slow	43/102 (42.2%)	58/99 (58.6%)	101/201 (50.3%)
Fast	59/102 (57.8%)	41/99 (41.4%)	100/201 (49.8%)
Slope ALSFRS-R, points per mo	0.69 [0.42–1.18]	0.56 [0.33–0.98]	0.62 [0.37–1.10]
ALSFRS-R, sum score	36.2 ± 6.6	37.5 ± 6.2	36.9 ± 6.4
SVC, %	83.2 ± 18.2	81.7 ± 20.0	82.4 ± 19.1
SEIQoL, sum score	69.4 ± 19.2	66.3 ± 21.9	67.9 ± 20.6
CNAQ, sum score	29.0 [27.0–31.0]	29.0 [26.0–31.0]	29.0 [27.0–31.0]

Data are mean ± standard deviation, n (%), n/N (%), or median [interquartile range].
[a]Time from onset of first symptoms until randomization.
[b]Time from diagnosis until randomization.
[c]Progression rate as defined by a slope in ALSFRS-R score (cutoff = 0.62 points/mo = median).
ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; BMI = body mass index; CNAQ = Council of Nutrition Appetite Questionnaire; SEIQoL = Schedule for the Evaluation of Individual Quality of Life; SVC = slow vital capacity.

All randomized patients who received at least 1 dose of trial treatment and had at least 1 available postbaseline assessment were analyzed for efficacy and safety (full analysis set [FAS] and identical safety analysis set).

To investigate efficacy (confirmatory analysis), the 1-sided unstratified log-rank test was used to compare both treatment groups in terms of survival time, defined as time from randomization until death or study cutoff date (last patient's last visit plus 14 days). This means that the observation period was not a fixed number of days, but varied depending on the randomization date of each patient, that is, patients who were recruited first had a longer observation period than patients who were recruited later. Because the last event in both groups happened 28 months after randomization of the first patient, this point in time was used for determination of survival probability. This time-to-event study design has been described by Oellrich et al[31] and has been used in previous ALS studies, for example, the rasagiline[32] and pioglitazone[33] trials.

The statistical hypotheses in terms of the HR were $H_0 = \lambda_2/\lambda_1 \geq 1$ and $H_1 = \lambda_2/\lambda_1 < 1$, where λ_2/λ_1 is the HR, λ_1 denotes the hazard in the placebo group, and λ_2 denotes the hazard in the HCFD group. We assumed the HR to be constant. For patients who prematurely dropped out of the study, the survival time was treated as censored at the time of last information.

All secondary endpoints were analyzed descriptively; missing values were not replaced. For continuous data, the Wilcoxon rank sum test or the 2-sample *t* test was carried out for group comparisons. Group comparisons for time until tracheostomy or death were done using Kaplan–Meier plots and log-rank test. Group comparisons for categorical data were carried out using the chi-square test. For ALSFRS-R, SEIQoL, SVC, BMI, and CNAQ, the progression rates under therapy were calculated using the slopes from a univariate linear regression model separate for each patient.

We did further exploratory analyses of the primary endpoint (time until death for the first 6, 12, and 18 months since randomization) with Kaplan–Meier plots and log-rank test. All statistical tests for the exploratory analyses of the primary endpoint and for all secondary endpoints were performed 2-sided at a significance level of 5%. Additionally, we fitted Cox proportional hazard regression models to adjust for possible effects of age, sex, weight, BMI, onset of disease (bulbar vs spinal), and baseline progression rate on survival.

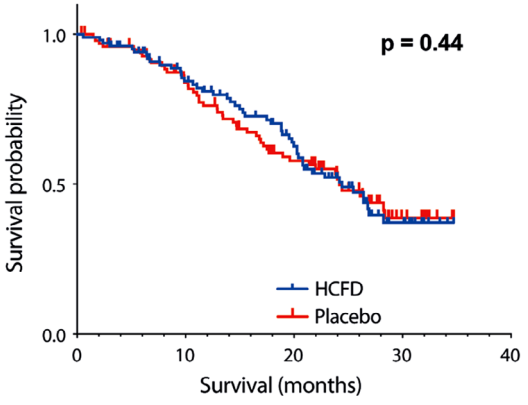
Because the rate of progression at baseline might affect response to intervention as shown by previous studies,[32,34] patients were stratified according to their initial progression rate in a post hoc analysis. The median of the initial ALSFRS-R slopes at baseline was used to define the cutoff. This method has been established in a previous clinical trial[32] and ensures 2 equally large groups, each comprising a clinically meaningful proportion of 50% of patients. Progression rate from first symptoms to baseline was calculated according to the formula (48[=maximum score] − score at randomization) / (date of randomization − date of first symptom). The median divided the slopes at a cutoff of a loss of 0.62 points of ALSFRS-R per month. Patients with a loss above 0.62 points of ALSFRS-R per month defined the population of fast-progressors, for which all outcome measures were analyzed. All results from the exploratory post hoc analyses should be interpreted as hypothesis-generating and not as proof of efficacy. No adjustment for multiple testing was made. Statistical analyses were done with SAS, version 9.4 (SAS Institute, Cary, NC).

Data Access, Responsibility, and Analysis

A.C.L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.Dr. conducted and is responsible for the data analysis.

Data Sharing

Individual participant data that underlie the results reported in this article, after deidentification (text, tables, and figures) as well as the study protocol will be available. Data will be available beginning 3 months and ending 5 years following article publication. Data will be shared with researchers who provide a methodologically sound proposal. Data will be shared for analyses to achieve the aims in the approved proposal. Proposals should be directed to albert.ludolph@rku.de; to gain access, data requestors will need to sign a data



Number at risk:

HCFD	102	91	71	57	33	13	0
Placebo	99	88	69	49	29	9	0

FIGURE 2: Survival, full analysis set (FAS). Kaplan–Meier survival curves are shown for overall survival. *p* = unadjusted log-rank *p* value. Survival after the whole study (time until death or study cutoff date) in the FAS population is shown, with confirmatory analysis (1-sided *p* value). HCFD = high-caloric fatty diet.

access agreement. Data are available for 5 years at https://www.uniklinik-ulm.de/neurologie.html.

Results

Between February 9, 2015 and July 11, 2016, 212 patients with ALS were screened at 12 study centers of the German ALS/MND network (Fig 1). The trial ended as planned according to protocol.

Two hundred seven patients were enrolled and randomly assigned to receive either placebo (n = 104) or HCFD (n = 103) after stratification based on site of onset (bulbar or spinal) and BMI (>21.75kg/m^2 vs ≤21.75kg/m^2). Six patients (5 in the placebo group and 1 in the HCFD group) did not take any dose of study medication and were therefore excluded from analysis. The remaining 201 patients (99 placebo, 102 HCFD) constituted the FAS.

TABLE 2. Primary and Secondary Outcomes (Full Analysis Set Population)

Outcome	High-Caloric Fatty Diet	Placebo	Total	*p*
Primary outcome				
Survival until death or study cutoff date	0.37 [0.25 to 0.49][a]	0.39 [0.27 to 0.51][a]	0.97 [−∞ to 1.44][b]	0.44[c]
Secondary outcomes				
Change in SVC,[d] slope in % per mo[e]	−1.72 [−3.70 to −0.48] n = 79	−1.71 [−3.23 to −0.50] n = 69	−1.72 [−3.35 to −0.49] n = 148	0.69[f]
Change in ALSFRS-R, slope in points per mo[e]	−0.89 [−0.59 to −1.40] n = 97	−0.83 [−0.46 to −1.40] n = 91	−0.86 [−0.49 to −1.40] n = 188	0.69[f]
Change in SEIQoL sum score,[g] slope in % per mo[e]	−0.10 [−0.68 to 0.60] n = 82	0.00 [−0.77 to 0.89] n = 74	−0.02 [−0.75 to 0.68] n = 156	0.55[f]
Change in CNAQ sum score,[g] slope in points per mo[e]	−0.16 [−0.41 to 0.08] n = 82	−0.08 [−0.33 to 0.03] n = 71	−0.10 [−0.34 to 0.05] n = 153	0.39[f]
Change in BMI,[g] slope of BMI per mo[e]	−0.06 [−0.21 to 0.04] n = 97	−0.09 [−0.27 to 0.00] n = 90	−0.08 [−0.24 to 0.02] n = 187	0.09[f]
Time until tracheostomy or death	0.70 [0.60 to 0.79][d] n = 102	0.58 [0.47 to 0.68][d] n = 99	0.94 [0.63 to 1.39][h] n = 201	0.74[i]

[a]Survival probability after 28 months [95% CI].
[b]HR [1-sided 97.5% CI].
[c]Log-rank test, 1-sided.
[d]Probability until month 18 (end of treatment).
[e]Median value [interquartile range].
[f]Wilcoxon rank-sum test.
[g]Dataset until month 18.
[h]HR [2-sided 95% CI].
[i]Log-rank test, 2-sided.
ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; BMI = body mass index; CI = confidence interval; CNAQ = Council of Nutrition Appetite Questionnaire; HR = hazard ratio; SEIQoL = Schedule for the Evaluation of Individual Quality of Life; SVC = slow vital capacity.

Baseline characteristics of both study groups are displayed in Table 1. Before randomization, HCFD patients showed a higher median loss of ALSFRS-R score per month compared to placebo patients (0.69 [interquartile range (IQR) = 0.42–1.18] vs 0.56 [IQR = 0.33–0.98]). Consistently, there were more patients above the median progression rate in the HFCD group than in the placebo group. All other factors were similar in both groups.

Fifty-three patients (26.4%) terminated the study before completion of their 18-month follow-up and were documented as dropouts. There were 31 dropouts in the HCFD group and 22 in the placebo group. Fifty-six patients (33 in the placebo group and 23 in the HCFD group) died during study participation, and 97 patients (48 in the placebo group and 49 in the HCFD group) died by the study cutoff date.

The primary efficacy endpoint at study end showed no significant difference between placebo and HCFD in terms of survival (time to death or study cutoff date). The survival probability after 28 months was 0.39 (95% confidence interval [CI] = 0.27–0.51) in the placebo group, and 0.37 (95% CI 0.25–0.49) in the HCFD group. The HR was 0.97, 1-sided 97.5% CI = $-\infty$ to 1.44, $p = 0.44$ (Cox proportional hazard regression model; Fig 2, Table 2). After adjusting for baseline progression rate, there was still no significant difference ($p = 0.40$, HR = 1.20, 2-sided 95% CI = 0.80–1.80, Cox proportional hazard regression model analysis for survival time as outcome and time, treatment group, and ALSFRS-R baseline progression rate as predictors). The results of the Cox proportional hazard regression models showed that younger patients, patients with higher weight at baseline, patients with higher BMI, and patients with lower baseline progression rate had better survival (data not shown).

There was no difference between placebo and HCFD for all secondary efficacy endpoints: change of

TABLE 3. Safety Analysis (FAS Population)

Adverse Event	High-Caloric Fatty Diet, n = 102	Placebo, n = 99	Total, n = 201
Dysphagia	25 (24.5)	24 (24.2)	49 (24.4)
Respiratory failure	17 (16.7)	18 (18.2)	35 (17.4)
Constipation	10 (9.8)	10 (10.1)	20 (10.0)
Diarrhea	9 (8.8)	6 (6.1)	15 (7.5)
Dyspnea	9 (8.8)	9 (9.1)	18 (9.0)
Fall	9 (8.8)	14 (14.1)	23 (11.4)
Nausea	9 (8.8)	10 (10.1)	19 (9.5)
Pneumonia	9 (8.8)	8 (8.1)	17 (8.5)
Nasopharyngitis	7 (6.9)	6 (6.1)	13 (6.5)
Bronchitis	6 (5.9)	5 (5.1)	11 (5.5)
Disease progression	6 (5.9)	7 (7.1)	13 (6.5)
Infection	6 (5.9)	1 (1.0)	7 (3.5)
Urinary tract infection	6 (5.9)	3 (3.0)	9 (4.5)
Depression	1 (1.0)	5 (5.1)	6 (3.0)
SAEs	54 (52.9)	57 (57.7)	111 (55.2)
AEs	86 (84.3)	87 (87.9)	173 (86.1)
Deaths during study participation	23 (22.5)	33 (33.3)	56 (27.9)
Deaths until end of trial	49 (48.0)	48 (48.5)	97 (48.3)

Data are given as n (%). The table presents all AEs that occurred in >5% of patients in at least 1 of the treatment groups in the FAS (identical to the safety analysis set). Additionally, summary information about AEs, SAEs, and deaths is given.
AE = adverse event; FAS = full analysis set; SAE = serious adverse event.

TABLE 4. Patient Characteristics at Baseline: Subgroups of Patients according to Progression Rates

Characteristic	Progression Rate ≤ 0.62 Points on ALSFRS-R per mo Upfront Randomization			Progression Rate > 0.62 Points on ALSFRS-R per mo Upfront Randomization		
	High-Caloric Fatty Diet, n = 43	Placebo, n = 58	Total, n = 101	High-Caloric Fatty Diet, n = 59	Placebo, n = 41	Total, n = 100
Age, yr[a]	62.0 ± 10.8	61.2 ± 10.9	61.5 ± 10.8	62.7 ± 11.3	64.2 ± 10.1	63.3 ± 10.8
Sex						
Female	16 (37.2%)	19 (32.8%)	35 (34.7%)	25 (42.4%)	20 (48.8%)	45 (45.0%)
Male	27 (62.8%)	39 (67.2%)	66 (65.3%)	34 (57.6%)	21 (51.2%)	55 (55.0%)
Weight, kg[a]	72.9 ± 10.5	75.3 ± 13.3	74.3 ± 12.2	73.7 ± 14.1	73.1 ± 14.0	73.4 ± 14.0
BMI, kg/m^2[a]	24.4 ± 2.8	24.6 ± 3.4	24.5 ± 3.1	25.4 ± 5.0	24.9 ± 3.7	25.2 ± 4.5
BMI ≤21.75, kg/m^2	7 (16.3%)	11 (19.0%)	18 (17.8%)	11 (18.6%)	8 (19.5%)	19 (19.0%)
BMI > 21.75, kg/m^2	36 (83.7%)	47 (81.0%)	83 (82.2%)	48 (81.4%)	33 (80.5%)	81 (81.0%)
Onset						
Bulbar	9 (20.9%)	13 (22.4%)	22 (21.8%)	20 (33.9%)	16 (39.0%)	36 (36.0%)
Spinal	34 (79.1%)	45 (77.6%)	79 (78.2%)	39 (66.1%)	25 (61.0%)	64 (64.0%)
Duration of disease, mo[b,c]	23.2 [16.4–33.4]	19.8 [14.6–31.3]	20.7 [15.3–31.8]	10.5 [8.0–15.8]	10.1 [7.9–15.4]	10.1 [7.9–15.7]
Time since diagnosis, mo[b,d]	8.0 [5.7–18.9]	6.6 [3.1–10.2]	7.5 [4.4–15.9]	4.0 [2.0–7.1]	3.9 [2.1–8.4]	3.9 [2.1–8.4]
Certainty of diagnosis						
Definite	4 (9.3%)	5 (8.6%)	9 (8.9%)	15 (25.4%)	11 (26.8%)	26 (26.0%)
Probable	16 (37.2%)	19 (32.8%)	35 (34.7%)	25 (42.4%)	20 (48.8%)	45 (45.0%)
Laboratory-supported probable	16 (37.2%)	21 (36.2%)	37 (36.6%)	15 (25.4%)	8 (19.5%)	23 (23.0%)
Possible	4 (9.3%)	6 (10.3%)	10 (9.9%)	4 (6.8%)	2 (4.9%)	6 (6.0%)
ALS subtype without 1st MN	3 (7.0%)	7 (12.1%)	10 (9.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Slope ALSFRS-R, points per mo[b]	0.41 [0.24–0.49]	0.37 [0.24–0.52]	0.37 [0.24–0.49]	1.13 [0.76–1.47]	1.10 [0.89–1.90]	1.11 [0.82–1.70]
ALSFRS-R, sum score[a]	39.4 ± 4.6	40.3 ± 5.0	39.9 ± 4.8	33.9 ± 6.9	33.7 ± 5.7	33.8 ± 6.4
SVC, %[a]	88.0 ± 16.6	87.0 ± 20.7	87.4 ± 19.0	79.6 ± 18.6	74.3 ± 16.7	77.4 ± 18.0
SEIQoL, sum score[a]	68.5 ± 19.3	70.1 ± 19.3	69.4 ± 19.2	70.1 ± 19.4	60.5 ± 24.5	66.3 ± 21.9
CNAQ, sum score[b]	29.0 [27.0–31.0]	30.0 [26.0–31.0]	29.0 [27.0–31.0]	29.0 [27.0–31.0]	29.0 [26.0–30.0]	29.0 [26.5–30.0]

[a]Mean ± standard deviation.
[b]Median [interquartile range].
[c]Time from onset of first symptoms until randomization.
[d]Time from diagnosis until randomization.
ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; BMI = body mass index; CNAQ = Council of Nutrition Appetite Questionnaire; MN = motor neuron; SEIQoL = Schedule for the Evaluation of Individual Quality of Life; SVC = slow vital capacity.

ALSFRS-R, SVC, BMI, SEIQoL, and CNAQ (see Table 2). After adjusting for baseline progression rate, there was still no significant difference for the ALSFRS-R (p = 0.26, regression coefficient for treatment group b = −1.08, 2-sided 95% CI = −2.96 to 0.79, linear mixed effects regression model analysis for the time course of

ALSFRS-R as outcome and time, treatment group, and baseline progression rate as predictors). The results from both the CNAQ and the nutrition questionnaire did not indicate any change of eating habits caused by the study intervention in either group. Survival curves equalizing tracheostomy (n = 4) with death revealed similar results as the primary endpoint survival.

HCFD was well tolerated, and most adverse events were due to progression of the disease (eg, dysphagia, dyspnea, or respiratory failure) rather than HCFD treatment (Table 3). Frequencies of adverse events and serious adverse events as well as laboratory safety variables were comparable between both groups. Frequencies of minor gastrointestinal adverse events (eg, vomiting, dyspepsia, or reflux) were slightly more frequent in the HCFD group. There was no difference with regard to creatine kinase serum levels at each time point (V2–V4) between HCFD and placebo.

Because recent studies[32,34] revealed an effect of edaravone and rasagiline on the subgroup of fast-progressing patients exclusively, we stratified patients according to their initial progression rate in a post hoc analysis. We used the median of the initial ALSFRS-R slopes at baseline (slope between the onset of disease and trial randomization) to define the cutoff. The median divided the slopes at a cutoff of a loss of 0.62 points of ALSFRS-R per month between onset of first symptom and baseline.

In the subgroup of fast-progressing patients (n = 100), the placebo and HCFD groups did not differ in their baseline characteristics (Table 4) with the exception of the SEIQoL. We found a significantly prolonged survival in the HCFD group after 18 months, the end of study intervention (Fig 3A). Survival probability was 0.38 (95% CI = 0.21–0.54) in the placebo group and 0.62 (95% CI = 0.47–0.74) in the HCFD group. The HR was 0.50, 2-sided 95% CI = 0.27–0.92, p = 0.02, Cox proportional hazard regression model. In the subgroup of slow progressors (loss of ALSFRS-R ≤ 0.62 per month at baseline), we found no difference with regard to survival (see Fig 3B; p = 0.50, Cox proportional hazard regression model, HR = 1.36, 2-sided 95% CI = 0.56–3.34). The stratified log-rank test (stratified by baseline progression rate, slow and fast progressors) showed a significantly prolonged survival for the HCFD group compared to placebo for the subgroup of fast progressors (p = 0.026, Cox proportional hazard regression model for survival time as outcome and treatment group and slow- vs fast-progressing patients as predictors, HR = 0.55, 2-sided 95% CI = 0.33–0.92).

Furthermore, loss of body weight was reduced in the HCFD group if compared to placebo in the subgroup of fast-progressing patients. Patients in the HCFD group lost 0.10 (IQR = −0.04 to 0.25) points of BMI per month during the intervention, whereas placebo patients lost 0.28 (0.01–0.44; p = 0.02, Wilcoxon rank sum test; median difference = −0.14, 2-sided 95% CI for the median difference = −0.26 to −0.02).

No effect on other outcome measures (eg, vital capacity, quality of life, CNAQ) was found in this population (data not shown).

Furthermore, we found no difference between HCFD and placebo for the subgroups of patients with high and low BMI at baseline (cutoff: median) or patients with spinal or bulbar onset with regard to survival.

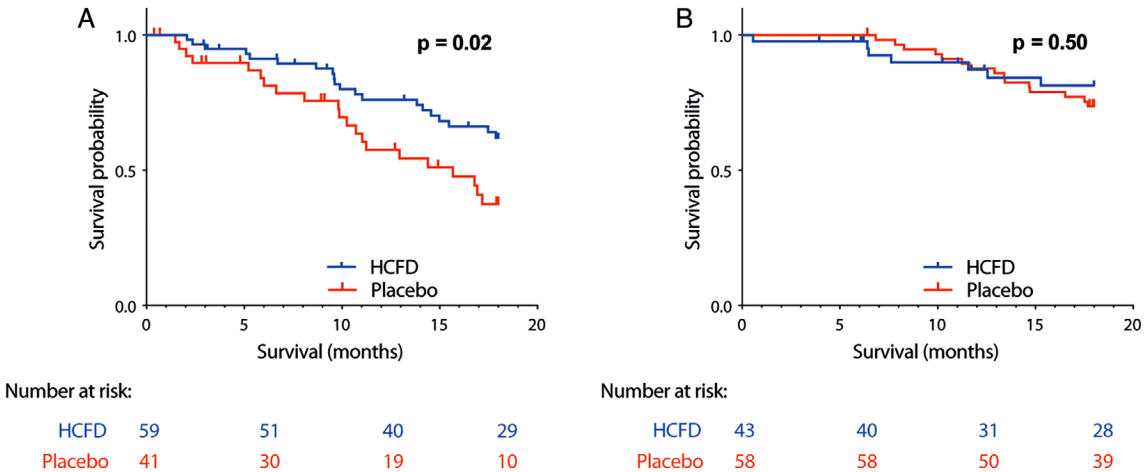


FIGURE 3: Survival in fast-progressing and slow-progressing patients. Kaplan–Meier survival curves for overall survival are shown. p = unadjusted log-rank p value. Survival after 18 months (intervention period) is shown in the subgroups of fast-progressing patients (patients with a decline in Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised [ALSFRS-R] score of >0.62 per month [median]; A) and slow-progressing patients (patients with a decline in ALSFRS-R score of ≤0.62 per month [median]; B), post hoc analysis (2-sided p value). HCFD = high-caloric fatty diet.

Discussion

HCFD was hypothesized to be disease-modifying in ALS, as has been suggested by a pilot clinical trial[26] and by preclinical animal studies.[24] Although the administration of HCFD in addition to riluzole was found to be safe in patients with ALS, there was no difference between placebo and HCFD groups in the primary outcome measure survival (time to death or study cutoff date). We also did not find significant differences with regard to secondary outcome parameters, such as function (ALSFRS-R), body weight, and SVC, which had previously been linked with hypercholesterinemia.[35] Therefore, the results do not provide evidence of a disease-modifying effect for HCFD in the whole ALS population studied, although such an effect cannot be excluded, considering the CI of the HR for the primary endpoint survival.

Driven by the results from recent studies,[32,34] the subgroup of fast-progressing patients was analyzed post hoc. In this subgroup, we identified a significant positive effect on survival and, importantly, a stabilization of weight, suggesting target engagement in this subgroup. As these are post hoc results, they have to be confirmed by another randomized controlled study specifically designed for this large subgroup of patients.

We cannot determine whether the higher calorie intake or an increased fat consumption is responsible for the treatment effect in this subgroup. Further studies are needed to provide more insight on dose–response relationships and the effect of food composition on efficacy and tolerability.

The results again highlight the importance of considering the progression rate of patients, as the effect of interventions seems to be dependent on this characteristic of the disease. We suggest that future clinical studies should feature a lead-in phase to accurately measure prebaseline disease progression and consequently stratify according to progression rates.

The compliance in this trial was lower than in previous ALS trials, as there was a dropout rate of 26%, which is double the rate of other ALS trials. For example, in the recent rasagiline trial done by the same group, there was a dropout rate of 13%.[32] Analysis of documented reasons for dropouts revealed that only few patients quit the study due to intolerance of the study medication. Dropouts were also not caused by adverse events or imminent death due to disease progression. Patients gave a wide variety of reasons, which were predominantly associated with the effort required by the study. In this context, we hypothesized that compliance may be lower for a nutritional intervention compared to studies with drugs. It might be hard to believe that a nutritional intervention could be an effective treatment for a devastating disease like ALS. However, this has to be elaborated further by a follow-up trial.

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Author Contributions

A.C.L., J.Do., J.S., L.D., and J.Dr. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. A.C.L., J.Do., J.S., L.D., and J.Dr. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

A.C.L. reports that the dietary supplement used in this study was provided at a cost reduction of 15% by Nutricia (Erlangen, Germany). All other authors have nothing to report.

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