

## Supplementary Online Content

Witzel S, Maier A, Steinbach R, et al; German Motor Neuron Disease Network (MND-NET). Safety and effectiveness of long-term intravenous administration of edaravone for treatment of patients with amyotrophic lateral sclerosis. *JAMA Neurol*. Published online January 10, 2022. doi:10.1001/jamaneurol.2021.4893

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eAppendix. Analysis of Potential Short-term Efficacy

### Methods

In subjects with both short- and long-term follow-up data, we computed a separate ALSFRS-R slope (disease progression rate in score points lost per month) for the first 24 weeks by excluding ALSFRS-R scores assessed after more than 24 weeks. Afterward, we compared the short-term ALSFRS-R slopes from the first 24 weeks to the long-term ALSFRS-R treatment slopes from the entire follow-up by calculating absolute deviations and applying the Wilcoxon Signed Rank Test. Additionally, we compared short-term disease progression in patients treated with edaravone and controls using an independent sample Mann-Whitney U Test.

### Results

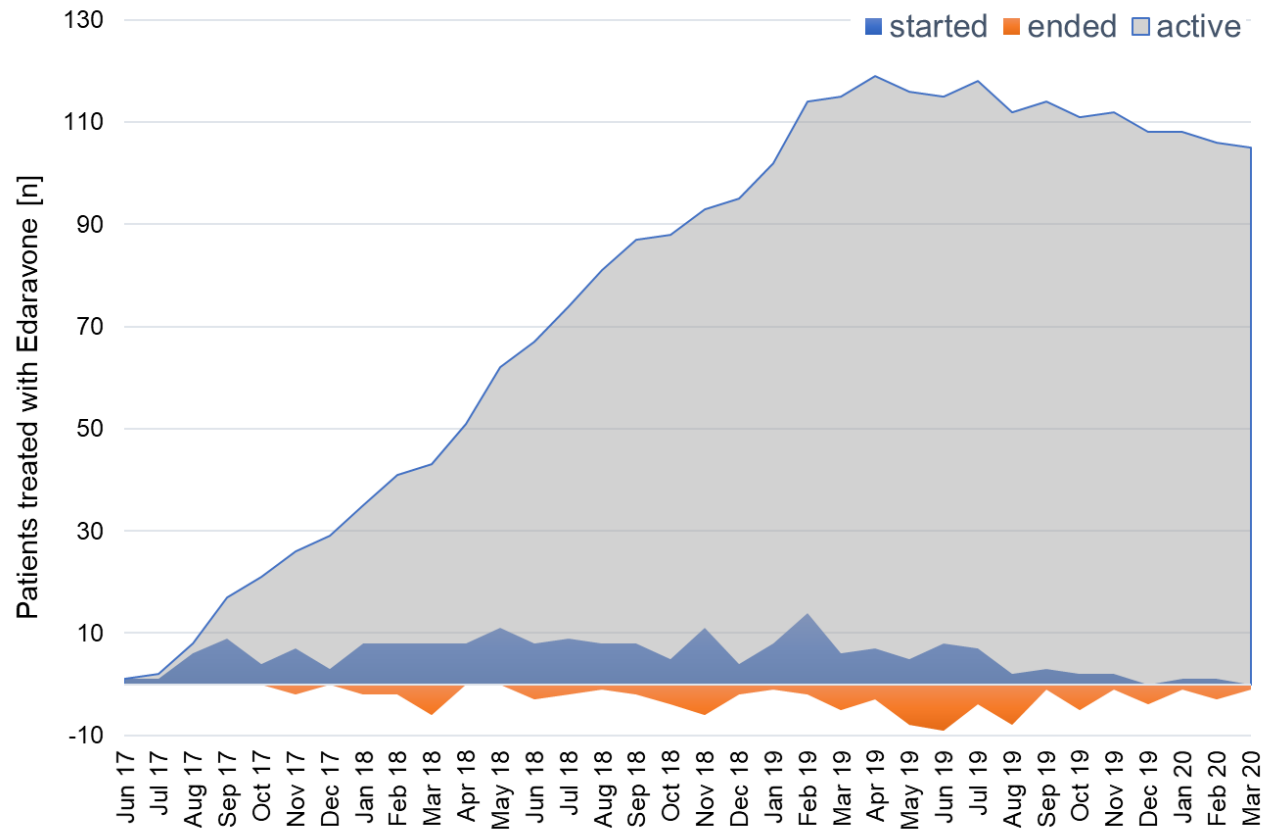
100 out of 116 patients on edaravone (86%) and 93 out of 116 controls (80%) in the propensity-score-matched sample were followed up for more than 24 weeks. In 92 of these patients, one or more ALSFRS-R scores were assessed within the first 24 weeks (5.5 months) after baseline. In these patients, the slopes during the first 24 weeks did not differ from the entire follow-up.

Overall (n=92)	first 24 weeks: -0.91 pt/m (IQR -1.74 to -0.29); entire follow-up: -0.99 pt/m (IQR -1.48 to -0.48); p=0.56.
Edaravone (n=62)	first 24 weeks: -0.91 pt/m (IQR -1.73 to -0.27); entire follow-up: -1.00 pt/m (IQR -1.50 to -0.56); p=0.94.
Controls (n=30)	first 24 weeks: -0.78 pt/m (IQR -1.94 to -0.29); entire follow-up: -0.88 pt/m (IQR -1.28 to -0.41); p=0.29.

Directly comparing short-term disease progression in patients treated with edaravone to controls we found no significant differences (edaravone: -0.91 pt/m; 95%CI [-0.62, -1.21]; controls: -0.78 pt/m; 95%CI [-0.43, -1.55]; p=0.92).

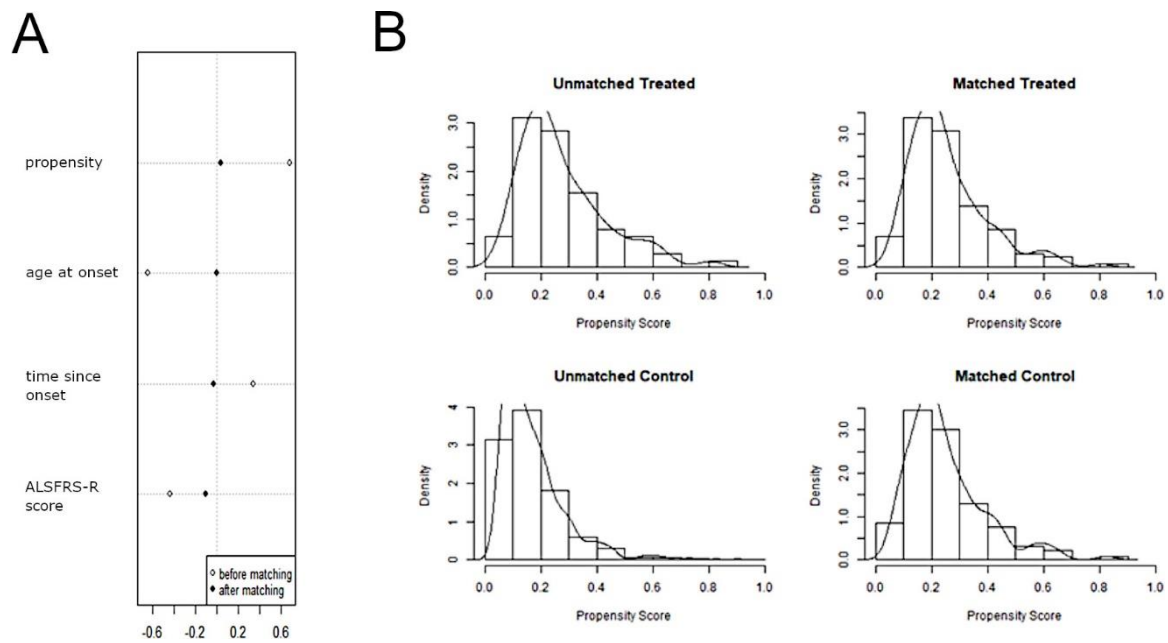
### Conclusion

This analysis indicates no clinically relevant differences between short-term and long-term ALSFRS-R slopes in our study. It suggests that edaravone treatment was not associated with a temporary short-term benefit in our study population.



**eFigure 1. Treatment evolution in the German Motor Neuron Disease Network**

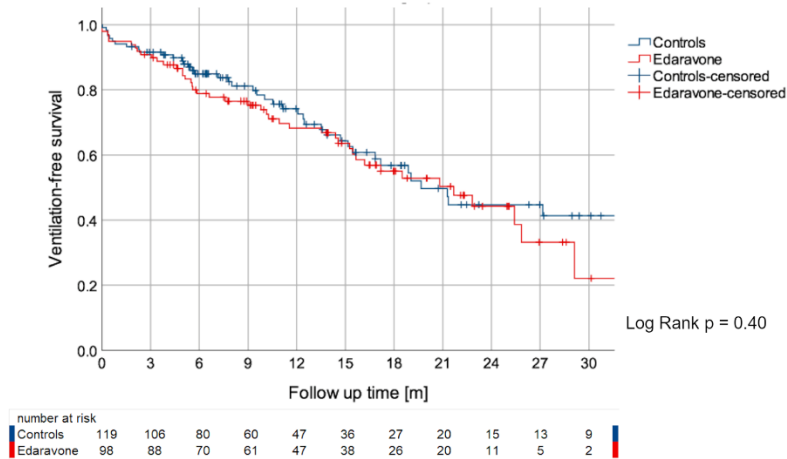
The panel shows a stacked line chart reporting the number of patients who started edaravone treatment (blue), ended treatment (orange), and under active treatment (grey) in the corresponding month. The total number of patients with active treatment steadily increased up to a maximum of 119 in April 2019 and decreased after the EMA application for edaravone was withdrawn in May 2019.



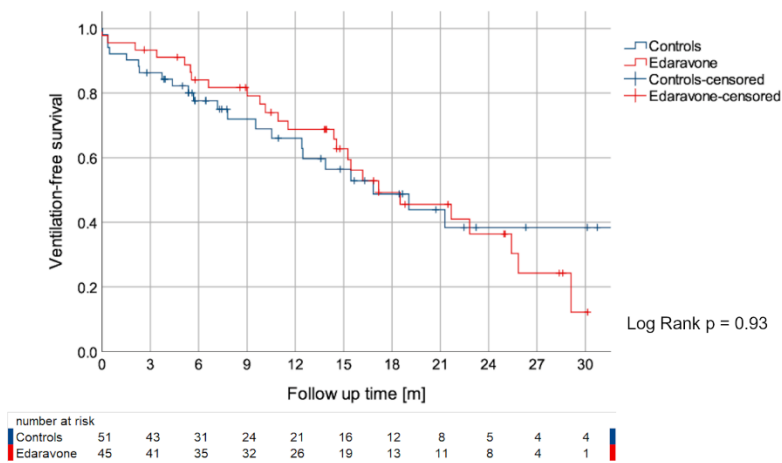
## eFigure 2. Effects of Propensity Score Matching

Scheme **A** is a dot-plot of standardized mean differences (Cohen's  $d$ ) for all covariates before and after matching. Scheme **B** shows the distribution of propensity scores of ALS patients treated with edaravone ("treated") and ALS patients not treated with edaravone ("control") before and after matching with overlaid kernel density estimate.

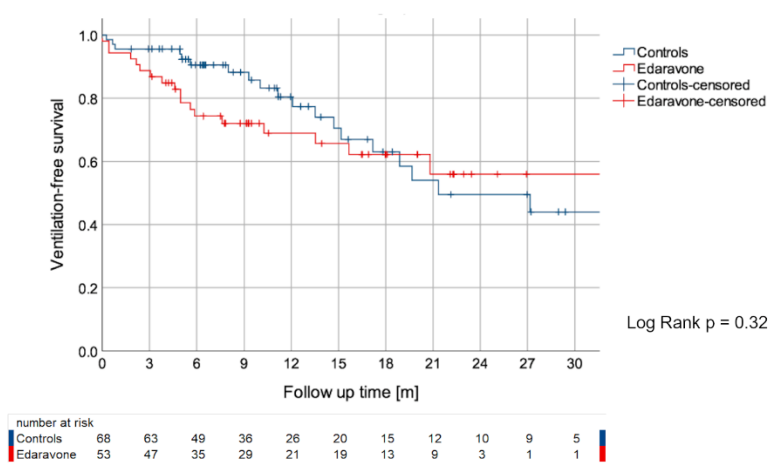
### A all patients



### B EFAS patients

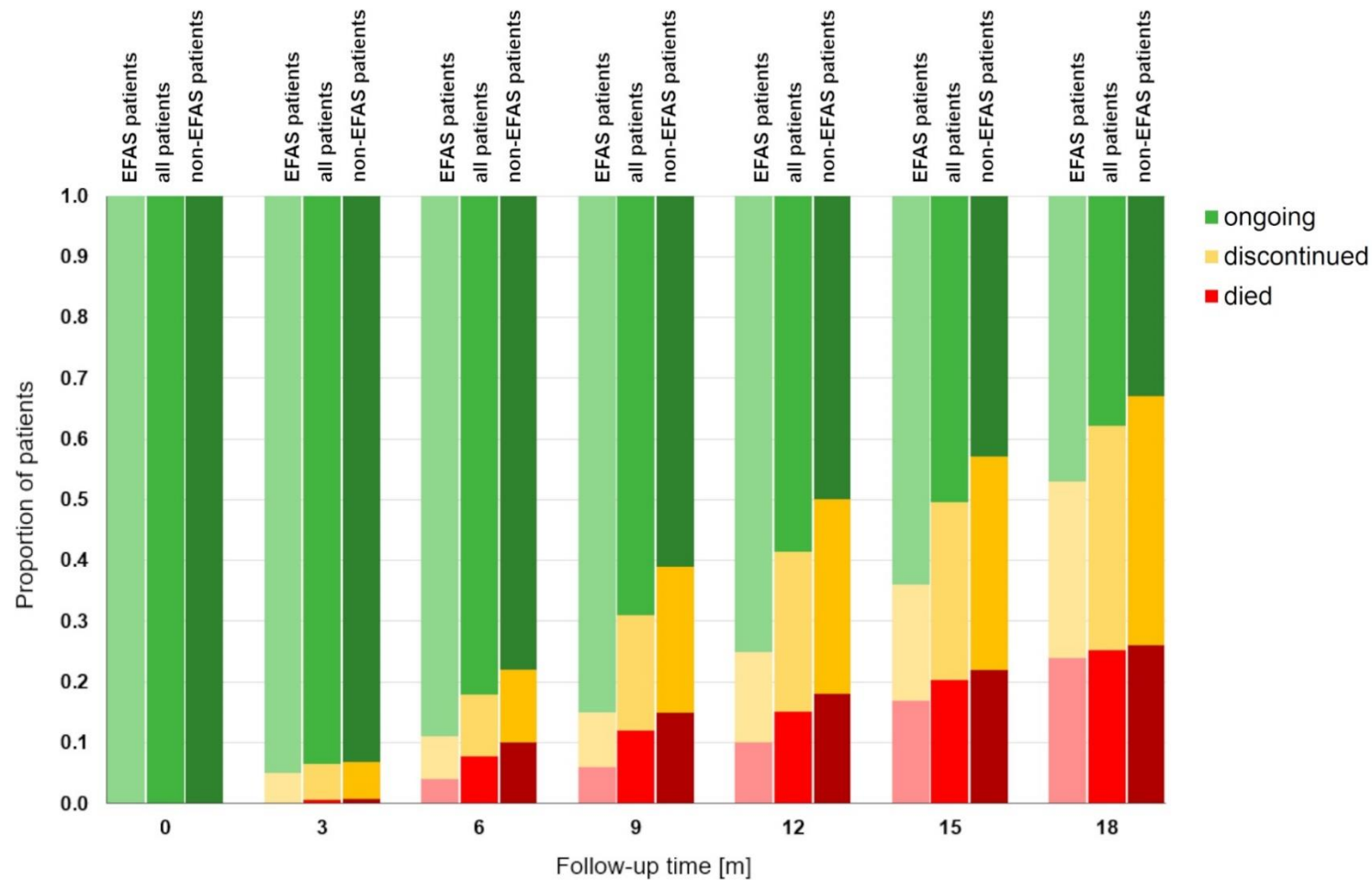


### C non-EFAS patients



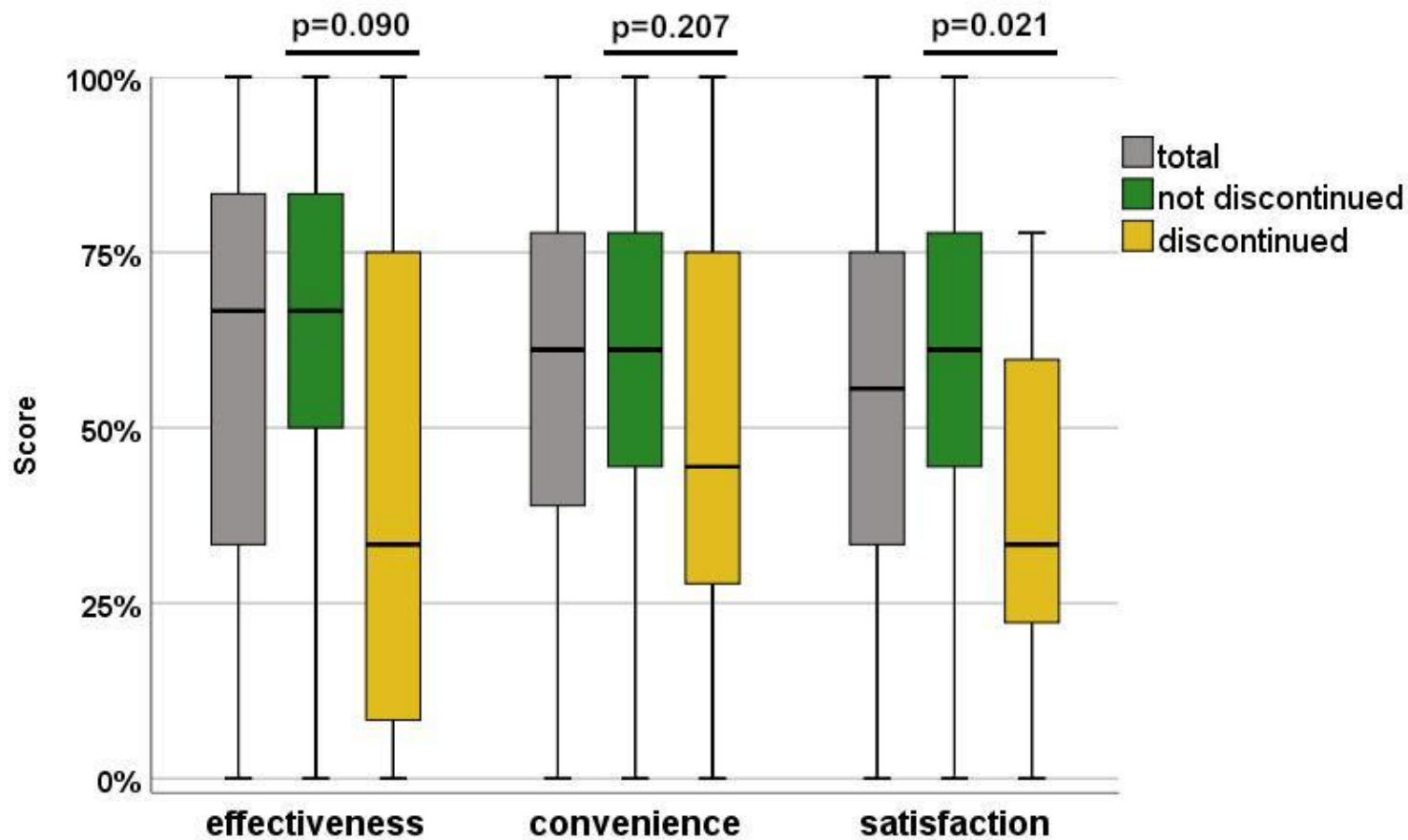
## eFigure 3. Ventilation-Free Survival

Panels show Kaplan Meier plots for ventilation-free survival during follow-up for all patients, EFAS patients, and non-EFAS patients in the propensity-score-matched sample for survival analysis. Patients already using ventilation at baseline ( $n=39$  (15%)) were excluded from this analysis. If not using ventilation and not deceased, patients were censored at the end of follow-up. Abbreviations: EFAS = potentially eligible for MCI186-19 study; non-EFAS = non-eligible for MCI186-19 study



#### eFigure 4. Edaravone Treatment Adherence

This stacked bar chart displays at three-month intervals the proportion of patients treated with edaravone who died (red), discontinued treatment (yellow), and with ongoing treatment (green). Patients with ongoing therapy were considered for an interval if the treatment duration was sufficient at the moment of analysis. Bars represent all edaravone patients (middle bar), EFAS patients (left bar), and non-EFAS patients (right bar). Abbreviations: EFAS = potentially eligible for MCI186-19 study; non-EFAS = non-eligible for MCI186-19 study



**eFigure 5. TSQM-9 Results in Patients Treated With Edaravone**

Box and whisker plots show median (central line), IQR (boxes), and 1.5×IQR (whiskers) of the patients' therapy evaluation in the three TSQM-9 dimensions: effectiveness, convenience, and global satisfaction. A higher total score is equivalent to higher satisfaction. In total, 68 patients answered the questionnaire (n=53 continuous therapy with edaravone (ongoing or died) / n=15 discontinued).