Safety and efficacy of rasagiline as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomised, double-blind, parallel-group, placebo-controlled, phase 2 trial

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Summary

Background Rasagiline, a monoamine oxidase B inhibitor with neuroprotective potential in Parkinson's disease, has shown a disease-modifying effect in the SOD1-Gly93Ala low-expressing mouse model of amyotrophic lateral sclerosis, both alone and in combination with riluzole. We sought to test whether or not rasagiline 1 mg/day can prolong survival in patients with amyotrophic lateral sclerosis also receiving riluzole.

Methods Patients with possible, probable, or definite amyotrophic lateral sclerosis were enrolled to our randomised, placebo-controlled, parallel-group, double-blind, phase 2 trial from 15 German network for motor neuron diseases (MND-NET) centres (university hospitals or clinics). Eligible patients were aged at least 18 years, had onset of progressive weakness within the 36 months before the study, had disease duration of more than 6 months and less than 3 years, and had a best-sitting slow vital capacity of at least 50%. After a 4-week screening period, eligible patients were randomly assigned (1:1) to receive either rasagiline (1 mg/day) or placebo in addition to riluzole (100 mg/day), after stratification for site of onset (bulbar or spinal) and study centre. Patients and all personnel assessing outcome parameters were masked to treatment allocation. Patients were followed up 2, 6, 12, and 18 months after randomisation. The primary endpoint was survival time, defined as the time to death or time to study cutoff date (ie, the last patient's last visit plus 14 days). Analyses of primary outcome and safety measures were done in all patients who received at least one dose of trial treatment (intention-to-treat population). The trial is registered with ClinicalTrials.gov, number NCT01879241.

Findings Between July 2, 2013, and Nov 11, 2014, 273 patients were screened for eligibility, and 252 patients were randomly assigned to receive rasagiline (n=127) or placebo (n=125). 126 patients taking rasagiline and 125 taking placebo were included in the intention-to-treat analysis. For the primary outcome, the survival probability at the end of the study was 0·43 (95% CI 0·25–0·59) in the rasagiline group (n=126) and 0·53 (0·43–0·62) in the placebo group (n=125). The estimated effect size (hazard ratio) was 0·91 (one-sided 97·5% CI –infinity to 1·34; p=0·31). Rasagiline was well tolerated, and most adverse events were due to amyotrophic lateral sclerosis disease progression rather than treatment; the most frequent of these were dysphagia (32 [25%] taking rasagiline *vs* 24 [19%] taking placebo) and respiratory failure (25 [20%] *vs* 31 [25%]). Frequency of adverse events were comparable between both groups.

Interpretation Rasagiline was safe in patients with amyotrophic lateral sclerosis. There was no difference between groups in the primary outcome of survival, although post-hoc analysis suggested that rasagiline might modify disease progression in patients with an initial slope of Amyotrophic Lateral Sclerosis Functional Rating Scale Revised greater than 0·5 points per month at baseline. This should be confirmed in another clinical trial.

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Introduction

Amyotrophic lateral sclerosis is a neurodegenerative disease, simultaneously affecting upper, cortical motor neurons, and lower, bulbar and spinal motor neurons. The median survival after onset is 2–3 years, and death is usually due to respiratory insufficiency and progressive muscle weakness. Few therapeutic options exist for patients with amyotrophic lateral sclerosis: riluzole prolongs survival by a few months,[1] and edaravone appears to improve functional scores of a small subset of patients. The formal pathogenesis of the disease is not well understood,[2] which might have contributed to the failure of recent clinical trials. In particular, neuroanatomical studies show that

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for randomised, placebo-controlled trials in patients with amyotrophic lateral sclerosis published up to April 14, 2018, using the terms "amyotrophic lateral sclerosis", "motor neuron disease", "motor neurone disease", "ALS", or "MND", with no language restrictions. We identified only riluzole and edaravone as drugs able to change the natural history of the disease. Rasagiline, a monoamine oxidase B inhibitor, is therapeutically used for the symptomatic treatment of Parkinson's disease, and is considered to be a disease-modifying compound. The drug dose-dependently increases survival in a standard rodent model of amyotrophic lateral sclerosis (low-expressing SOD1-Gly93Ala) alone and in addition to riluzole.

Added value of the study

This prospective, randomised, double-blind, placebo-controlled trial assessed the safety and efficacy of rasagiline in patients with amyotrophic lateral sclerosis. The intention-to-treat analysis did not show rasagiline to have a therapeutic effect. The post-hoc analysis suggested that the drug positively effects function and survival in a subpopulation of patients who have fast-progressing amyotrophic lateral sclerosis (patients with an initial slope of Amyotrophic Lateral Sclerosis Functional Rating Scale Revised of more than 0.5 points per month between onset of first symptoms and baseline).

Implications of all the available evidence

The intention-to-treat analysis was negative, suggesting that rasagiline is not broadly disease modifying in amyotrophic lateral sclerosis. The post-hoc analysis suggests a potential therapeutic effect on function and survival in about 50% of patients with amyotrophic lateral sclerosis (faster progressors). This observation should be confirmed in a second, specifically designed clinical trial before its use can be considered in clinical practice. This study also strongly calls for a stratification of future trials according to fast and slow progressors to identify subgroups most likely to benefit from a treatment.

amyotrophic lateral sclerosis preferentially affects phylogenetically young neuronal networks, which are not present in rodents,[2–4] and staging studies indicate the cortex and corticoefferent tracts have a primary role.[2,5] Amyotrophic lateral sclerosis is widely accepted to be a multisystem disease, and previously underappreciated neuronal types might be crucial in disease progression.[2]

Rasagiline is a monoamine oxidase B (MAO-B) inhibitor, and is generally acknowledged as a disease-modifying drug in Parkinson's disease.[6,7] By inhibiting MAO-B, rasagiline reduces dopamine and, to a lesser extent, serotonin catabolism, thereby increasing the availability of dopamine and serotonin for neurotransmission. Rasagiline is effective as a symptomatic treatment for Parkinson's disease,[6] and evidence supports a potential disease-modifying effect at a dose of 1 mg/day.[7] Rasagiline was effective in prolonging survival a low-expressing mouse model of amyotrophic lateral sclerosis (SOD1-Gly93Ala),[8] suggesting its therapeutic potential in this disease. An open-label, single-arm, clinical trial of 2 mg rasagiline per day in 36 patients with amyotrophic lateral sclerosis indicated that rasagiline intake could modify exploratory biomarkers, such as mitochondrial defects and apoptotic markers in the blood, but was not powered to detect disease-modifying effects.[9]

We did an investigator-initiated trial of rasagiline in patients with amyotrophic lateral sclerosis, through the German network for motor neuron diseases (MND-NET). To this aim, we based our protocol on that of a previously published study,[10] to verify the hypothesis of potential efficacy of rasagiline in amyotrophic lateral sclerosis as an add-on therapy to riluzole.

For the **study protocol** see https://www.uniklinik-ulm.de/fileadmin/default/Kliniken/Neurologie/Downloads/Studienzentrum/RAS-ALS-Protocol.pdf

Methods

Study design and participants

This study was a randomised, double-blind, parallel-group, placebo-controlled trial of rasagiline as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis at 15 MND-NET centres (university hospitals and clinics) in Germany. The study was done in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guideline for Good Clinical Practice, and European Union Clinical Trials Directive, and the applicable local regulations. The Competent Ethics Committee of the University of Ulm, Germany, in consultation with the involved local ethics committees approved the study protocol (approval number 378/12). For review of safety results, an independent data safety and monitoring board was established before the start of the study; this board reviewed the safety data every 3 months during the trial, and recommended to the sponsor whether or not to continue, modify, or terminate the trial.

The trial protocol can be accessed online.

Patients with possible, probable (clinically or laboratory supported), or definite amyotrophic lateral sclerosis, according to the revised version of the El Escorial World Federation of Neurology criteria, were considered for enrolment into the study.[11]

Included patients were aged at least 18 years, had onset of progressive weakness within 36 months before the study, had disease duration of more than 6 months and less than 3 years (with disease onset defined as date of first muscle weakness, excluding fasciculation, and cramps), and a best-sitting slow vital capacity (a measure of respiratory function) of at least 50%. We included women of childbearing age who were non-lactating and surgically

sterile, or used a highly effective method of birth control and had a negative pregnancy test. All included patients had been treated with 100 mg riluzole per day for at least 3 months before inclusion. Exclusion criteria were participation in another clinical study within the preceding 12 weeks; tracheostomy or assisted ventilation during the preceding 3 months; gastrostomy; any medical condition known to have an association with motor neuron dysfunction that might confound the diagnosis of amyotrophic lateral sclerosis; presence of any life-threatening disease or impairment likely to interfere with functional assessment; current treatment with sympathomimetic agents (including pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine); current treatment with analgesics with serotonergic properties (eg, meperidine, tramadol, methadone, and propoxyphene); patients on serotonin reuptake inhibitors; patients on dextromethorphan, St John's wort or cyclobenzaprine; current treatment with other MAO inhibitors (selective or non-selective); current treatment with serotonin noradrenalin reuptake-inhibitors or tricyclic and tetracyclic antidepressants; confirmed hepatic insufficiency or abnormal liver function (aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal); renal insufficiency (serum creatinine >2·26 mg/dL); evidence of major psychiatric disorder or clinically evident dementia; known hypersensitivity to the study drug; or likely to be non-cooperative or not comply with the trial requirements (as assessed by the investigator), or unable to be reached in emergency. All patients gave written informed consent.

The initial study protocol (version 1.0) excluded the intake of any antidepressants. To avoid unnecessary medical and ethical conflicts, this exclusion criterion was revised (protocol version 2.0) and only antidepressants contraindicated by the summary of product characteristics of rasagiline were prohibited.

Randomisation and masking

At the randomisation visit, each eligible patient was randomly assigned (1:1) to one of the two treatment groups, and received the next consecutive randomisation number according to their stratum from a block of randomisation numbers per site. The code was broken at the end of study (ie, the last patient's last visit plus 14 days). The randomisation list was generated by 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 non-predictable. The randomisation was stratified according to site of disease onset (ie, bulbar or spinal), and was separate for each study site.

The trial was double-blinded; patients and site personnel were masked to treatment allocation. Study medication (identical rasagiline and placebo tablets) was manufactured by Teva Pharmaceutical Industries (Kfar Saba, Israel), and masked by the pharmacy of the University Hospital Ulm, Germany, according to the randomisation list generated by the Institute of Epidemiology and Medical Biometry, University of Ulm, Germany. Each patient medication bottle was sent together with the sealed unmasking codes to the sites. The site investigator ensured each patient was provided with the study medication box of the correct randomisation number.

Procedures

Study participants received standard therapy (100 mg riluzole) plus 1 mg rasagiline (rasagiline group) or placebo (placebo group) per day. Enrolled patients underwent a screening phase, which lasted up to 4 weeks, and an 18-month treatment phase. Clinical and physical examinations (outcome measures), blood sampling, and drug compliance were recorded at on-site visits (2, 6, 12, and 18 months after baseline visit). Bodyweight and functional status (including non-invasive ventilation and Amyotrophic Lateral Sclerosis Functional Rating Scale Revised [ALSFRS-R]) were recorded 1, 3, 9, and 15 months after baseline visit via telephone. The investigators observed patients for adverse events and instructed patients to report any events. A 14-day follow-up window after the patient had routinely or prematurely terminated the study was included for adverse events. Long-term survival status of all study participants was collected at the end of the study (ie, the last patient's last visit plus the 14-day follow-up for adverse events).

Outcomes

The primary endpoint was survival time—ie, the time from randomisation until death or until the study cutoff date (ie, the last patient's last visit plus 14 days). Secondary efficacy outcomes were change of total score of ALSFRS-R, change of slow vital capacity, and change in individual quality of life according to the Schedule for Evaluation of Individual Quality of Life (SEIQoL); in all cases, change was defined as the difference from baseline. The increasing use of tracheostomy was observed during the study; thus, the secondary outcome of time until tracheostomy or death from baseline was added to the statistical analysis plan, which was finalised before unmasking and the start of analysis. Safety endpoints included the terms and frequency of reported adverse events and serious adverse events, and safety laboratory parameters (clinical chemistry and haematology) and vital signs. Values for safety laboratory parameters were compared with both the appropriate normal ranges and ranges of potential clinical concern as defined by the treating study physician.

Statistical analysis

We calculated the sample size on the basis of a comparison of two survival curves with the one-sided

log-rank test. We made the following assumptions: type I error 0·025, power 0·80, recruiting time 6 months, length of follow-up 18 months, 18 months survival rate of 70% in the control group, and 18 months survival rate of 85% in the rasagiline group. Under the assumption of equal numbers of patients in each group, this scenario required 106 patients in each group. A previous trial (NCT00690118) reported a patient dropout of about 15%, and screening failure in about 10% of patients. Thus, we aimed to include 250 patients.

We analysed the study population according to the intention-to-treat principle. All patients randomly assigned to study groups who received at least one dose of trial treatment were analysed for safety and efficacy. To investigate efficacy, we used the one-sided unstratified log-rank test to compare both treatment groups. The statistical hypotheses in terms of the hazard ratio (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 control group, and λ_2 denotes the hazard in the rasagiline group. We assumed the HR to be constant. We tested the null hypothesis with the log-rank test. We set the type I error to $\alpha=0\cdot025$ (one sided). To estimate the treatment effect, we used the HR, including the one-sided 97·5% CI.

All secondary endpoints (change of total score of ALSFRS-R, change in SEIQoL, change of slow vital capacity, and time until tracheostomy or death) were prespecified to be analysed in an exploratory manner. We used the Wilcoxon rank-sum test for group comparisons of continuous data, Kaplan-Meier plots and the log-rank test for group comparisons for time until tracheostomy or death, and the χ^2 test or Fisher's exact test for group comparisons of categorical data.

For ALSFRS-R, we calculated the progression rate from first symptoms to baseline according to the formula (48 [ie, maximum ALSFRS-R sum score]–score at randomisation)/(date of randomisation–date of first symptom). For ALSFRS-R, SEIQoL, and slow vital capacity, we calculated the progression rates under therapy (ie, decline from time of randomisation until end of study treatment) by use of the slopes from a univariate linear regression model separate for each patient and each endpoint. All available data were used in each patient for these calculations. Missing values in ALSFRS-R, SEIQoL, and slow vital capacity were not replaced.

We did further exploratory analyses of the primary endpoint (time until death for the first 6, 12, and 18 months since randomisation) with Kaplan-Meier plots and log-rank test. We did all statistical tests for the exploratory analyses of the primary endpoint and for all secondary endpoints two-sided at a significance level of 5%. The results from the exploratory analyses should be interpreted as hypothesis generating and not as proof of efficacy. Additionally, we fitted Cox proportional hazard regression models to adjust for possible effects of age, sex, weight, and onset of disease (bulbar *vs* spinal) on the primary endpoint.

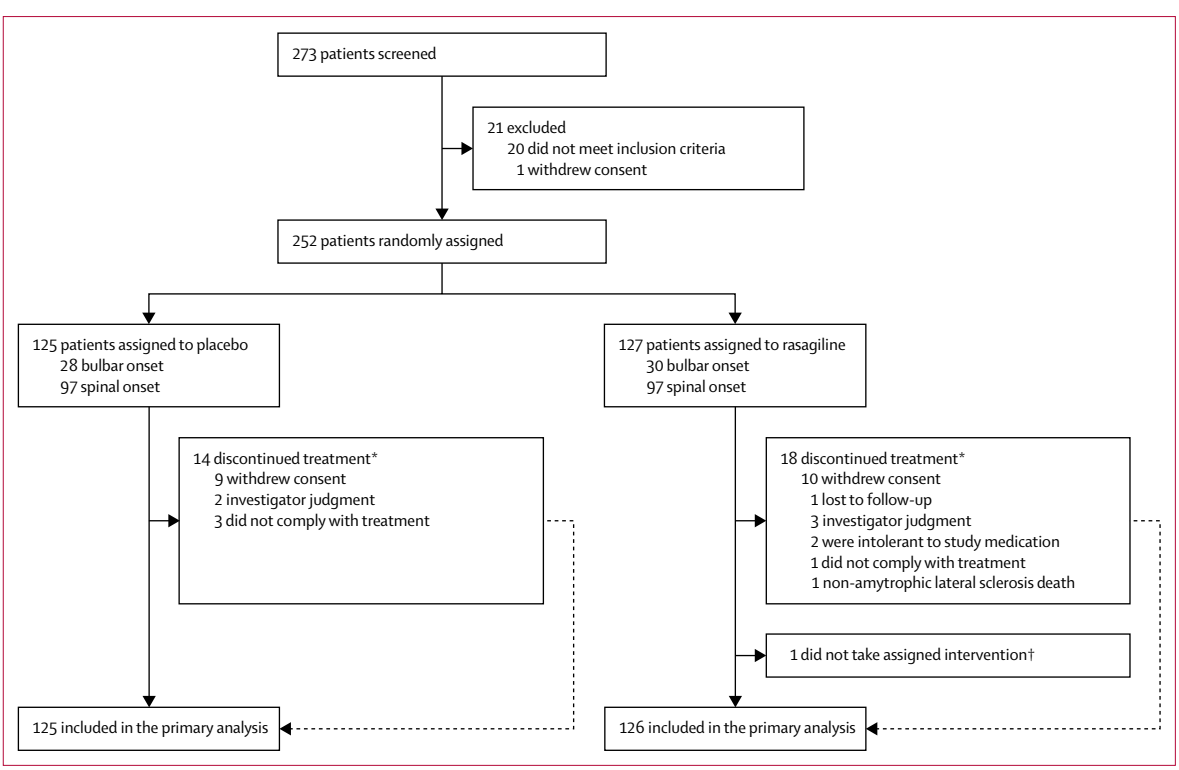

Figure 1: **Trial profile**
*Survival time for discontinued study participants was censored at the time of discontinuation and used in the primary analysis. †One patient in the rasagiline group did not take the allocated intervention and was excluded from the primary analysis.

For the post-hoc analysis, we chose a cutoff of more than 0·5 points per month loss of ALSFRS-R slope at the time of randomisation (ie, baseline); we also analysed all endpoints of the intention-to-treat approach in this group. To define the slope of ALSFRS-R at baseline, we collected the date of first symptoms post hoc. The study sites provided information for 90% of randomised patients. For dropouts, survival time was treated as censored at the time of dropout.

Statistical analyses were done using SAS, version 9.4.

The trial is registered with ClinicalTrials.gov, number NCT01879241.

Role of the funding source

This study is an investigator-initiated trial of the German MND-NET, with institutional support from Teva Pharmaceutical Industries. Study medication was provided by Teva. Teva had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication, but reviewed the final version of the Article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 2, 2013, and Nov 11, 2014, 273 patients with amyotrophic lateral sclerosis were screened at 15 study centres of the German MND-NET (figure 1). 252 patients were enrolled, and randomly assigned to receive either placebo (n=125) or rasagiline (n=127) after stratification based on site of onset (bulbar or spinal). One patient in the rasagiline group did not take any dose of study medication and was therefore excluded from the intention-to-treat analysis. The study cutoff date (ie, the last patient's last visit plus 14 days) was April 28, 2016.

Baseline characteristics of both study groups were similar (table 1); both groups of patients were of similar age, body-mass index, and functional status as measured by the ALSFRS-R and slow vital capacity. The sex distribution in the treatment groups was different (rasagiline 68 [54%] men *vs* 58 [46%] women; placebo 84 [67%] men *vs* 41 [33%] women). The overall ALSFRS-R progression rates at randomisation (baseline) within the treatment groups were similar (placebo [n=113] median 0·52 [IQR 0·32–0·88; range 0·04–3·69]; rasagiline [n=113] median 0·52 [IQR 0·36–0·84; range 0·14–5·19]; p=0·63, Wilcoxon rank-sum test). 32 patients terminated the study before completion of their 18-month follow-up. One of these patients died, but the death was determined not to be related to amyotrophic lateral sclerosis or to the study treatment. The other 31 patients were documented as dropouts. We had 17 dropouts in the rasagiline group and 14 in the placebo group.

75 patients died during study participation, and 101 patients died by the study cutoff date. More patients died in the placebo group (n=41) than in the rasagiline group (n=34) during study participation, but the number of deaths at the study cutoff date (ie, the last patient's last visit plus 14 days) was similar in both groups (placebo n=51, rasagiline n=50).

The primary efficacy endpoint at end of the study showed no difference between placebo and rasagiline groups in terms of survival (time to death or study cutoff date). The survival probability was 0·53 (95% CI 0·43–0·62) in the placebo group, and 0·43 (0·25–0·59)

	Rasagiline (n=126)	Placebo (n=125)	Total (n=251)
Age, years	60·1 (11·2)	60·4 (10·2)	60·2 (10·7)
Sex	..	..	..
Women	58 (46%)	41 (33%)	99 (39%)
Men	68 (54%)	84 (67%)	152 (61%)
Body-mass index, kg/m²	25·2 (3·8)	25·6 (3·6)	25·4 (3·7)
Onset	..	..	..
Bulbar	30 (24%)	28 (22%)	58 (23%)
Spinal	96 (76%)	97 (78%)	193 (77%)
Duration of disease, months*	19·0 (11·7), n=114	17·9 (9·7), n=113	18·5 (10·8), n=227
Certainty of diagnosis	..	..	..
Definite	24 (19%)	22 (18%)	46 (18%)
Probable	60 (48%)	68 (54%)	128 (51%)
Laboratory-supported probable	31 (25%)	26 (21%)	57 (23%)
Possible	11 (9%)	9 (7%)	20 (8%)
Smoker during study	21 (17%)	27 (22%)	48 (19%)
Progression†	..	..	..
Slow	50/113 (44%)	54/113 (48%)	104/226 (46%)
Normal to fast	63/113 (56%)	59/113 (52%)	122/226 (54%)
ALSFRS-R, sum score	37·9 (5·6)	38·3 (5·3)	38·1 (5·4)
Slow vital capacity, %	84·1% (19·2%)	85·4% (17·0%)	84·8% (18·1%)
SEIQoL, sum score	67·1 (19·5)	68·3 (20·6)	67·7 (20·0)

Data are mean (SD), n (%), or n/N (%). ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised. SEIQoL=Schedule for Evaluation of Individual Quality of Life. *Onset of first symptoms has been collected post hoc. †Normal to fast progression rate as defined by a slope of ALSFRS-R of more than 0·5 points per month, defined post hoc.

Table 1: **Patient characteristics at baseline (intention-to-treat population)**

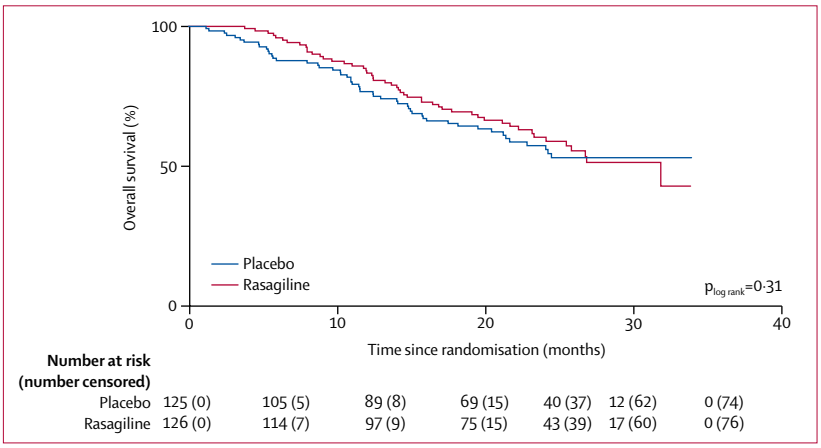

Figure 2: **Survival (time until death or study cutoff date) in intention-to-treat population**
Kaplan-Meier survival curves for overall survival. $p_{log\ rank}$=unadjusted log-rank p value.

in the rasagiline group. The HR was 0·91, one-sided 97·5% CI –infinity to 1·34, p=0·31 (figure 2, table 2).

There was no difference between the rasagiline and placebo groups for all secondary efficacy endpoints in the intention-to-treat population: change of total score of ALSFRS-R, slow vital capacity, sum score of SEIQoL, and time until tracheostomy or death (table 2). There was also no difference between groups in incidence of tracheostomy during the study period (rasagiline n=9, 7%; placebo n=8, 6%; p=0·81).

Rasagiline was well tolerated, and most adverse events were due to amyotrophic lateral sclerosis disease progression (eg, dysphagia, dyspnoea, or respiratory failure), rather than rasagiline treatment (table 3). Frequency of adverse events and serious adverse events, and laboratory safety variables, were comparable between both groups. No suspected unexpected serious adverse reactions were reported.

In exploratory analyses, rasagiline had a significant effect on survival (time to death) within the first 6 months of study treatment (HR –1·16 [95% CI –2·17 to –0·15]; log-rank p=0·0178), but this effect was not observed at 12-month or 18-month follow-up (data not shown), or at the end of the study. The results of the Cox proportional hazard regression models showed that younger patients and patients with higher weight at baseline had better survival (data not shown).

Since the rate of progression might affect drug response, 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 randomisation) to define the cutoff. The median divided the slopes at a cutoff of a loss of 0·5 points of ALSFRS-R per month between onset of first symptom and baseline. This cutoff at baseline predicted a functional decline of roughly 1 point per month in untreated patients during the disease course (between onset of first symptom and death).[12] Besides this difference in progression rate in patients in this subgroup (n=122), both the rasagiline and placebo groups did not differ in their baseline characteristics (appendix). We also found a disease-modifying effect of rasagiline at all timepoints in the group of normal to fast-progressing patients, because ALSFRS-R decline was significantly reduced in this subgroup (table 4; appendix). This protective effect was substantiated by a similar protective effect of rasagiline on survival until month 12 (appendix). No effect on vital capacity or quality of life was found in this population (data not shown).

	Rasagiline (n=126)	Placebo (n=125)	Total (n=251)	p value
Primary outcome				
Survival until death or study cutoff date	0·43 (0·25 to 0·59)*	0·53 (0·43 to 0·62)*	0·91 (–infinity to 1·34)†	0·31‡
Secondary outcomes				
Change in ALSFRS-R, points per month§	0·95 (0·41 to 1·28)	1·02 (0·48 to 1·53)	0·97 (0·46 to 1·48)	0·32¶
Change in SVC, % per month§	2·07 (0·65 to 4·08)	1·78 (0·49 to 4·23)	1·83 (0·59 to 4·14)	0·82¶
Change SEIQoL sum score, % per month§	0·03 (–0·67 to 0·95	0·24 (–0·27 to 1·22)	0·12 (–0·49 to 1·16)	0·20¶
Survival until tracheostomy or death	0·37 (0·20 to 0·55)*	0·48 (0·38 to 0·58)*	0·92 (0·64 to 1·33)‖	0·65**

Data are median (IQR) unless otherwise stated. ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised. HR=hazard ratio. SVC=slow vital capacity. SEIQoL=Schedule for Evaluation of Individual Quality of Life. *Survival probability (95% CI). †HR (one-sided 97·5% CI). ‡Log-rank test (one sided). §Dataset until month 18. ¶Wilcoxon rank-sum test. ‖HR (two-sided 95% CI). **Log-rank test (two sided).

Table 2: **Primary and secondary outcomes**

	Rasagiline (n=126)	Placebo (n=125)	Total (n=251)	p value*
Dysphagia	32 (25%)	24 (19%)	56 (22%)	0·24
Respiratory failure	25 (20%)	31 (25%)	56 (22%)	0·35
Dyspnoea	21 (17%)	17 (14%)	38 (15%)	0·50
Falls	13 (10%)	20 (16%)	33 (13%)	0·18
Contusion	10 (8%)	7 (6%)	17 (7%)	0·46
Headache	9 (7%)	8 (6%)	17 (7%)	0·82
Nasopharyngitis	9 (7%)	10 (8%)	19 (8%)	0·80
Pneumonia	9 (7%)	8 (6%)	17 (7%)	0·82
Vertigo	9 (7%)	6 (5%)	15 (6%)	0·43
Depression	7 (6%)	12 (10%)	19 (8%)	0·23
Hypoventilation	7 (6%)	4 (3%)	11 (4%)	0·36
Rash	7 (6%)	2 (2%)	9 (4%)	0·17†
Constipation	6 (5%)	7 (6%)	13 (5%)	0·77
Back pain	3 (2%)	8 (6%)	11 (4%)	0·12

Data are n (%). Table presents all adverse events that occurred in six or more patients (across both treatment groups) in the intention-to-treat population. *Calculated using χ^2 test unless otherwise specified. †Fisher's exact test.

Table 3: **Adverse events**

	Rasagiline (n=61)	Placebo (n=58)	Total (n=119)	p value*
Dataset until month 6	1·01 (0·58–1·67)	1·37 (0·89–2·68)	1·17 (0·66–1·83)	0·0103
Dataset until month 12	1·04 (0·67–1·66)	1·46 (1·10–2·24)	1·26 (0·79–1·97)	0·0099
Dataset until month 18	1·03 (0·65–1·66)	1·51 (1·16–2·35)	1·27 (0·74–1·97)	0·0051

Data are median (IQR); post-hoc analysis. A progression rate of more than 0·5 points per month at baseline was predictive for a progression rate of more than 1·0 point per month later on. ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised. *Wilcoxon rank-sum test.

Table 4: **Change in ALSFRS-R in subgroup of normal-progressing to fast-progressing patients**

Discussion

Rasagiline was hypothesised to be a disease-modifying drug in amyotrophic lateral sclerosis, as has been shown in Parkinson's disease[6,7] and suggested by preclinical animal studies.[8] Although the administration of rasagiline in addition to riluzole was found to be safe in patients with amyotrophic lateral sclerosis in this study, there was no difference between placebo and rasagiline groups in the primary endpoint of survival (time to death at study cutoff date). However, in an exploratory analysis, rasagiline exerted a positive effect on survival during the first 6 months in the intention-to-treat population

(p=0·0178). This effect at 6 months might have resulted from an inclusion bias characterised by a higher number of patients with fast-progressing disease in the placebo group than in the rasagiline group. Post-hoc stratifications revealed a protective potential in the subgroup of patients with normal to fast disease progression. This subgroup was well balanced between the rasagiline and placebo groups and is characterised by a median slope of ALSFRS-R of 1·51 in the placebo group during the 18-month treatment duration. All patients had a slower progression of disease from onset of first symptoms until trial randomisation (plateau) than later on, when they developed faster disease progression. We used broad inclusion and exclusion criteria to support the enrolment of patients with fast-progressing amyotrophic lateral sclerosis (ie, a slow vital capacity of at least 50% of normal, and a disease duration of more than 6 months and less than 3 years). In the overall trial population, 53 (23%) study participants had a slow vital capacity between 50% and 75% and a disease duration of up to 24 months. This result might underlie the results of the post-hoc analysis, which showed 1 mg of rasagiline to slow disease progression in the subgroup of patients with normal to fast disease progression, both in terms of function and survival (table 4; appendix).

To date, only two drugs have shown positive effects in amyotrophic lateral sclerosis. Riluzole increases survival,[13] and is the only drug to have a protective effect in the global amyotrophic lateral sclerosis population. Edaravone, which was licensed as a disease-modifying drug in amyotrophic lateral sclerosis for the USA and Japan in 2017,[14] modifies the slope of ALSFRS-R in a subset of patients with amyotrophic lateral sclerosis. Here, our post-hoc results also suggest an effect of rasagiline on ALSFRS-R at 6, 12, and 18 months, and on survival at 6 months and 12 months. Our trial did not prespecify an analysis according to progression rate, and thus the evidence provided should be subject to caution. As was the case in previous studies of dexpramipexole,[15,16] post-hoc analysis[17] might contradict the primary analyses. Thus, a future clinical trial should be done to unambiguously establish whether rasagiline has therapeutic potential in patients with normal to fast-progressing amyotrophic lateral sclerosis. Another limitation of our study is that we do not include dose-response relationships, which could prove important because rasagiline exerted dose-dependent effects in Parkinson's disease, in a U-shaped fashion.[6,7] Rasagiline has several advantages, including oral intake, few side-effects, and previously documented use in a large population of patients with Parkinson's disease.

Besides a possible disease-modifying effect, our study has implications regarding trial design and interpretation in amyotrophic lateral sclerosis and neurodegenerative disorders. From our results, it appears mandatory that a careful analysis of disease progression rate should be done at trial inclusion to identify, and ideally stratify, patients with slow and fast progressing disease. Such prespecified stratification would especially be useful when early endpoints (eg, ALSFRS-R slope or survival at 6 months) are planned as primary outcomes. We suggest that progression rate should be part of the inclusion criteria in exploratory short trials. More generally, our results suggest that disease-modifying effects of drugs might be variable according to progression rate, and this should be taken into account along with dose-response.

In conclusion, this investigator-initiated trial of rasagiline did not show a disease-modifying effect in the primary analysis of survival (time to death or study cutoff date). Post-hoc analysis suggested rasagiline's protective potential in patients with normal to fast progression rate which should be confirmed in a future trial, and indicated that stratification for disease progression should be done in future clinical trials in amyotrophic lateral sclerosis.

Contributors

ACL, JS, JDo, LD, JDr, JHW, and JK conceived of and designed the study. ACL, JDo, JHW, UW, SP, TM, JG, BS, AE, AH, DZ, JP, ASW, TG, MTH, SWJ, and BG were study investigators. ACL, JS, JDo, LD, and JDr analysed and interpreted data. JK reviewed the safety of patients who had serious adverse events. All authors critically revised the manuscript.

Declaration of interests

ACL received grants from Teva Pharmaceutical Industries to support this study; and personal fees from Hoffmann-La Roche, Novartis, Desitin Pharma, Syneos Health, Teva Pharmaceutical Industries, Boehringer Ingelheim, Biogen, and Mitsubishi Pharma for consultancy services outside the submitted work. TM received personal fees for consultancy services outside the submitted work from Biogen, Teva Pharmaceutical Industries, Desitin Pharma, and grants and personal fees from Cytokinetics outside the submitted work. SP received compensation for consultancy services outside the submitted work from Cytokinetics, Teva Pharmaceutical Industries, and Desitin Pharma. All other authors declare no competing interests.

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