Clinical trial results:
Efficacy, Safety and Tolerability Study of 1 mg Rasagiline in Patients with Amyotrophic Lateral Sclerosis (ALS) Receiving Standard Therapy (Riluzole)

Summary

EudraCT number	2011-004482-32
Trial protocol	DE
Global end of trial date	28 April 2016

Results information

Result version number	v1 (current)
This version publication date	03 February 2021
First version publication date	03 February 2021

Trial information

Trial identification

Sponsor protocol code	RAS-ALS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01879241
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm
Sponsor organisation address	Albert-Einstein-Alle 29, Ulm, Germany, 89081
Public contact	Prof. Dr. A.C. Ludolph, Universitätsklinikum Ulm, 0049 07311771200, albert.ludolph@rku.de
Scientific contact	Prof. Dr. A.C. Ludolph, Universitätsklinikum Ulm, 0049 07311771200, albert.ludolph@rku.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2016
Global end of trial reached?	Yes
Global end of trial date	28 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy of rasagiline as add-on therapy to standard therapy with riluzole in patients with ALS compared to placebo in terms of survival (mortality exclusively defined as death).

Protection of trial subjects:

The study intervention was provided add on to standard therapy with riluzole. The frequency of study visits was in line with the number of visits under standard therapy. Hence, no additional burden to standard health care was constituted.

Background therapy:

The study intervention was provided add on to standard therapy with riluzole. Trial subjects were stable on standard therapy (100 mg riluzole per day) for at least 3 months before inclusion.

Evidence for comparator: -

Actual start date of recruitment	02 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 251
Worldwide total number of subjects	251
EEA total number of subjects	251

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	164
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 02 July 2013, and 11 November 2014, trial subjects were recruited at at 15 study centres of the German ALS/MND-NET.

Pre-assignment

Screening details:

273 patients with amyotrophic lateral sclerosis were screened, 20 did not meet inclusion criteria, 1 withdrew consent during screening process. Hence, 252 patients were randomly assigned to receive either placebo (n=125) or rasagiline (n=127). One patient assigned to rasagiline did not take any treatment and was hence excluded from FAS.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Rasagiline

Arm description:

1 mg rasagiline (study intervention) plus standard therapy (100 mg riluzole), per day

Arm type	Experimental
Investigational medicinal product name	Rasagiline mesilate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg rasagiline per day

Arm title	Placebo

Arm description:

Non-active substance (placebo) plus standard therapy (100 mg riluzole), per day

Arm type	Placebo
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Non-active substance (placebo), 1 tablet per day plus standard therapy (100 mg riluzole)

Number of subjects in period 1	Rasagiline	Placebo
Started	126	125
Completed	108	111
Not completed	18	14
Consent withdrawn by subject	10	9
Physician decision	3	2
Adverse event, non-fatal	2	-
did not comply with treatment	1	3
Non-amyotrophic lateral sclerosis death	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rasagiline
Reporting group description:	
1 mg rasagiline (study intervention) plus standard therapy (100 mg riluzole), per day	
Reporting group title	Placebo
Reporting group description:	
Non-active substance (placebo) plus standard therapy (100 mg riluzole), per day	

Reporting group values	Rasagiline	Placebo	Total
Number of subjects	126	125	251
Age categorical			
Units: Subjects			

Age continuous			
252 patients with ALS at the age of 30.7-81.8 years were randomly assigned to receive either placebo (n=125) or rasagiline (n=127). In the rasagiline group, one patient left study participation before starting the intervention since he did not take the assigned intervention as to why only 126 patients were included in the primary analysis.			
Units: years			
arithmetic mean	60.1	60.4	
standard deviation	± 11.2	± 10.2	-
Gender categorical			
251 patients with ALS were assigned to receive either placebo (n=125) or rasagiline (n=126). 99 (39%) of them were female, 152 (61%) were male.			
Units: Subjects			
Female	58	41	99
Male	68	84	152
ALSFRS-R			
Physical functioning of the patients before randomisation was measured with the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R). A maximum score of 48 indicates unimpaired functioning status.			
Units: Score			
arithmetic mean	37.9	38.3	
standard deviation	± 5.6	± 5.3	-
Slow vital capacity			
Respiratory functioning before randomisation was assessed by slow vital capacity (SVC). A best-sitting SVC of at least 50% was required for inclusion in the trial.			
Units: Percent			
arithmetic mean	84.1	85.4	
standard deviation	± 19.2	± 17.0	-
SEIQoL			
Individual quality of life before randomisation was measured according to the Schedule for Evaluation of Individual Quality of Life (SEIQoL). In an interview the five most important areas of life are extracted, their weight is calculated and they are evaluated in terms of satisfaction for each subject.			
Units: Score			
arithmetic mean	67.1	68.3	
standard deviation	± 19.5	± 20.6	-

End points

End points reporting groups	
Reporting group title	Rasagiline
Reporting group description:	
1 mg rasagiline (study intervention) plus standard therapy (100 mg riluzole), per day	
Reporting group title	Placebo
Reporting group description:	
Non-active substance (placebo) plus standard therapy (100 mg riluzole), per day	

Primary: Survival probability	
End point title	Survival probability
End point description:	
The primary objective of this trial was to investigate survival to evaluate the efficacy of rasagiline as add-on therapy to riluzole. Hence, the time from randomization until death or the end of trial was compared between the group receiving rasagiline and the placebo group. Reported is the survival probability (95% CI).	
End point type	Primary
End point timeframe:	
Time from baseline (date of randomization) until date of death or end of whole trial (last patient's last visit plus a 14-days safety follow-up.)	

End point values	Rasagiline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Probability				
number (confidence interval 95%)	0.43 (0.25 to 0.59)	0.53 (0.43 to 0.62)		

Statistical analyses

Statistical analysis title	Survival
Statistical analysis description:	
As a primary efficacy endpoint survival in terms of time to death or end of trial was assessed. The study population was analysed according to the intention-to-treat principle. The two treatment groups were compared using a one-sided unstratified log-rank test.	
Comparison groups	Rasagiline v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91

Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.34

Notes:

[1] - The primary efficacy endpoint survival at the end of the study did not show a significant difference between the group receiving treatment with rasagiline and the placebo group.

Secondary: Change in ALSFRS-R

End point title	Change in ALSFRS-R

End point description:

Changes in the ALSFRS-R were assessed and compared between the two groups to evaluate the benefit of rasagiline on physical functioning.

End point type	Secondary

End point timeframe:

Baseline (date of randomization) until end of participation (18 months or death)

End point values	Rasagiline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Points/month				
median (inter-quartile range (Q1-Q3))	0.95 (0.41 to 1.28)	1.02 (0.48 to 1.53)		

Statistical analyses

Statistical analysis title	Change in ALSFRS-R

Statistical analysis description:

Change in physical functioning in terms of ALSFRS-R, measured in points per month was evaluated by a Wilcoxon rank-sum test. No significant difference was found between the group receiving treatment with rasagiline and the placebo group (p=0.32).

Comparison groups	Rasagiline v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.32 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - The difference in change of ALSFRS-R score was not found significant between the rasagiline and the placebo group.

Secondary: Change in SVC

End point title	Change in SVC

End point description:

Changes in the slow vital capacity (SVC) were assessed in %/month to evaluate the benefit of rasagiline on respiratory function.

End point type	Secondary

End point timeframe:

Baseline (date of randomization) until end of trial participation (18 months after baseline)

End point values	Rasagiline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: percent/month				
median (inter-quartile range (Q1-Q3))	2.07 (0.65 to 4.08)	1.78 (0.49 to 4.23)		

Statistical analyses

Statistical analysis title	Change in SVC

Statistical analysis description:

To evaluate the benefit of rasagiline on respiratory function changes in slow vital capacity (SVC) were assessed in % per months as a secondary endpoint. No significant difference was found between the two groups.

Comparison groups	Rasagiline v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.82 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - The difference in change of SVC was found not significant between the group receiving rasagiline as treatment and the placebo group.

Secondary: Time to tracheostomy or death

End point title	Time to tracheostomy or death

End point description:

The time to tracheostomy or death was assessed as a secondary objective to evaluate the benefit of rasagiline. During their participation in this trial 9 patients in the rasagiline group (7%) and 8 patients in the placebo group (6%) underwent a tracheostomy. Reported is the survival probability for a tracheostomy or death (95% CI).

End point type	Secondary

End point timeframe:

Baseline until end of study participation (18 months after baseline)

End point values	Rasagiline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Probability				
number (confidence interval 95%)	0.37 (0.20 to 0.55)	0.48 (0.38 to 0.58)		

Statistical analyses

Statistical analysis title	Survival until tracheostomy or death

Statistical analysis description:

The survival probability for a tracheostomy during the study period or death was calculated and compared between the group receiving rasagiline as treatment and the placebo group.

Comparison groups	Rasagiline v Placebo
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.65
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Secondary: Change in SEIQoL

End point title	Change in SEIQoL

End point description:

Changes in SEIQoL score were assessed as % per months to evaluate benefit of rasagiline on the individual quality of life.

End point type	Secondary

End point timeframe:

Baseline (date of randomization) until end of participation (18 months or death)

End point values	Rasagiline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Percent/month				
median (inter-quartile range (Q1-Q3))	0.03 (-0.67 to 0.95)	0.24 (-0.27 to 1.22)		

Statistical analyses

Statistical analysis title	Change in SEIQoL

Statistical analysis description:

To evaluate the benefit of rasagiline for the individual quality of life changes in sum score of the SEIQoL were assessed in % per months as a secondary endpoint of the trial. No significant difference was found between the two groups. The analysis however shows nearly constant values over time with similar results for both groups.

Comparison groups	Rasagiline v Placebo

Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - The difference in change of SEIQoL was found not significant between the group receiving treatment with rasagiline and the placebo group.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Time from baseline to final visit (18 months) plus additional 14 days safety follow-up	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Rasagiline
Reporting group description: 1 mg rasagiline (study intervention) plus standard therapy (100 mg riluzole), per day	
Reporting group title	Placebo
Reporting group description: Non-active substance (placebo) plus standard therapy (100 mg riluzole), per day	

Serious adverse events	Rasagiline	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 126 (61.11%)	85 / 125 (68.00%)	
number of deaths (all causes)	34	41	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 126 (3.17%)	5 / 125 (4.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 126 (0.79%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	30 / 126 (23.81%)	24 / 125 (19.20%)	
occurrences causally related to treatment / all	0 / 30	0 / 24	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal			

disorders			
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 126 (19.05%)	31 / 125 (24.80%)	
occurrences causally related to treatment / all	0 / 26	0 / 35	
deaths causally related to treatment / all	0 / 10	0 / 19	
Dyspnoea			
subjects affected / exposed	21 / 126 (16.67%)	16 / 125 (12.80%)	
occurrences causally related to treatment / all	1 / 23	0 / 20	
deaths causally related to treatment / all	0 / 3	0 / 2	
Pneumonia			
subjects affected / exposed	8 / 126 (6.35%)	6 / 125 (4.80%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
Hypoventilation			
subjects affected / exposed	7 / 126 (5.56%)	4 / 125 (3.20%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 126 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 126 (0.79%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 126 (0.79%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2.39 %

Non-serious adverse events	Rasagiline	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 126 (60.32%)	73 / 125 (58.40%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 126 (9.52%)	16 / 125 (12.80%)	
occurrences (all)	16	23	
Contusion			
subjects affected / exposed	9 / 126 (7.14%)	5 / 125 (4.00%)	
occurrences (all)	9	9	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 126 (7.14%)	8 / 125 (6.40%)	
occurrences (all)	10	8	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 126 (7.14%)	6 / 125 (4.80%)	
occurrences (all)	9	7	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	3 / 126 (2.38%)	0 / 125 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	6 / 126 (4.76%)	7 / 125 (5.60%)	
occurrences (all)	6	7	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 126 (0.79%)	0 / 125 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	2 / 126 (1.59%)	1 / 125 (0.80%)	
occurrences (all)	2	2	
Pneumonia			

subjects affected / exposed occurrences (all)	1 / 126 (0.79%) 1	2 / 125 (1.60%) 3	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 7 / 126 (5.56%) 7	 1 / 125 (0.80%) 1	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	 6 / 126 (4.76%) 6	 10 / 125 (8.00%) 13	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 2 / 126 (1.59%) 2	 7 / 125 (5.60%) 7	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 9 / 126 (7.14%) 11	 10 / 125 (8.00%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2013	The initial study protocol (version 1.0, 26 November 2012) excluded the intake of any antidepressants. To avoid unnecessary medical and ethical conflicts, this exclusion criterion was revised (protocol version 2.0, 02 October 2013) and only antidepressants contraindicated by the summary of product characteristics of rasagiline were prohibited.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29934198