Clinical trial results:
A Phase 3, Multi-center, Open-label, Safety Study of Oral Edaravone Administered over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Summary

EudraCT number	2019-002108-41
Trial protocol	DE IT
Global end of trial date	07 October 2021

Results information

Result version number	v1 (current)
This version publication date	26 August 2023
First version publication date	26 August 2023

Trial information

Trial identification

Sponsor protocol code	MT-1186-A01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04165824
WHO universal trial number (UTN)	-
Other trial identifiers	Japan Registry of Clinical Trials (jRCT): jRCT2080224982

Notes:

Sponsors

Sponsor organisation name	Mitsubishi Tanabe Pharma America, Inc.
Sponsor organisation address	525 Washington Blvd, Suite 1100, Jersey City, United States, 07310
Public contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, regulatory@mt-pharma-eu.com
Scientific contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, regulatory@mt-pharma-eu.com

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	24 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2021
Global end of trial reached?	Yes
Global end of trial date	07 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of Oral Edaravone in subjects with ALS over 24 and 48 weeks.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice as required by the International Conference on Harmonization guidelines, applicable regional and local legislation, and standard operating procedures in place at Mitsubishi Tanabe Pharma America Inc and at the contracted vendor. All participants underwent screening aimed at minimizing the likelihood and impact of potential risks of MT-1186. In addition, regular safety monitoring during the study period for all participants ensured that any unanticipated effects of study participation were identified promptly and managed appropriately.
Risk minimization measures were also employed during the study as per the risk-benefit assessment for potential anticipated risks.
A participant was to be withdrawn from the study if ANY of the protocol specific withdrawal criteria were met including voluntary wish of participant to withdraw from further participation

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	United States: 71
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	185
EEA total number of subjects	26

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)	120
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment Started on 26 Nov 2019 and was completed on 29 Oct 2020, globally: USA, Canada, Germany, Italy, France, Japan
Subjects Screened: 216
Screen Failures: 31
Subjects Enrolled in Study: 185
Subjects who completed week 48: 139
Subjects who discontinued during week 48: 46

Pre-assignment

Screening details:

Subjects were screened globally following protocol specific inclusion and exclusion criteria
Subjects Screened: 216
Screen Failures: 31
Reason for Screen Failure
Study Entry Criteria Not Met (25)
Withdrawal by Subjects (2)
Covid 19 (4)

Period 1

Period 1 title	MT-1186-A01 (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	MT-1186

Arm description:

MT-1186 105mg (2 weeks On/Off)

Arm type	Experimental
Investigational medicinal product name	MT-1186
Investigational medicinal product code	
Other name	Edaravone
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

MT-1186 oral suspension (21 mg/mL) in amber multi-use bottles, adapters, and oral syringes were provided for each subject, for the duration of their participation in the study. Suspension bottles contained approximately 735 mg of MT-1186 in 35 mL for the first cycle and approximately 1050 mg of MT-1186 in 50 mL for Cycles 2 through 12.
All subjects enrolled received the following dose regimen:
* An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period.
* Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. Treatment cycles were every 4 weeks.
The dose of MT-1186 was taken after an overnight fast and subjects continued to fast at least 1 to 2 hours postdose before the next meal (eg, breakfast)

Number of subjects in period 1	MT-1186
Started	185
Completed	139
Not completed	46
Physician decision	1
Consent withdrawn by subject	17
Adverse event, non-fatal	23
Other	5

Baseline characteristics

Reporting groups

Reporting group title	MT-1186-A01

Reporting group description: -

Reporting group values	MT-1186-A01	Total	
Number of subjects	185	185	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	120	120	
From 65-84 years	65	65	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	66	66	
Male	119	119	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	177	177	
Unknown or Not Reported	5	5	

Subject analysis sets

Subject analysis set title	Full Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis Population:
Enrolled Population: The enrolled population set is all subjects who were found eligible and signed ICF to participate in the study.
Safety Analysis Population: The safety analysis population set is defined as all enrolled subjects who received at least 1 dose of oral edaravone
Pharmacokinetic (PK) Population: PK population includes all subjects who receive at least 1 dose of oral edaravone and who have at least 1 post-dose value for plasma concentration without important protocol deviations which may affect the PK of oral edaravone.

Reporting group values	Full Analysis		
Number of subjects	185		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	120		
From 65-84 years	65		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	66		
Male	119		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	177		
Unknown or Not Reported	5		

End points

End points reporting groups

Reporting group title	MT-1186
Reporting group description: MT-1186 105mg (2 weeks On/Off)	
Subject analysis set title	Full Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Analysis Population:
Enrolled Population: The enrolled population set is all subjects who were found eligible and signed ICF to participate in the study.
Safety Analysis Population: The safety analysis population set is defined as all enrolled subjects who received at least 1 dose of oral edaravone
Pharmacokinetic (PK) Population: PK population includes all subjects who receive at least 1 dose of oral edaravone and who have at least 1 post-dose value for plasma concentration without important protocol deviations which may affect the PK of oral edaravone.

Primary: Number of Participants with Treatment Emergent Adverse Events

End point title	Number of Participants with Treatment Emergent Adverse Events[1]

End point description:

End point type	Primary

End point timeframe:

48 Weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is a long-term, open-label safety study. As a result, no formal hypothesis testing is planned for this study. The long-term safety and tolerability of oral edaravone was evaluated in exploratory manner using descriptive statistics. For exploratory efficacy analysis, point estimates and their associated 95% Confidence Interval was presented.

End point values	MT-1186	Full Analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	185	185		
Units: Subjects				
Any TEAE	175	175		
Any TEAE Related to Study Treatment	46	46		
Any Severe TEAE	34	34		
Any TESAE	48	48		
TEAE Leading to Study Treatment Discontinuation	16	16		
Any TEAE Leading to Death	12	12		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Treatment Emergent Adverse Events

End point title	Number of Treatment Emergent Adverse Events[2]

End point description:

End point type	Primary

End point timeframe:

48 Weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study is a long-term, open-label safety study. As a result, no formal hypothesis testing is planned for this study. The long-term safety and tolerability of oral edaravone was evaluated in exploratory manner using descriptive statistics. For exploratory efficacy analysis, point estimates and their associated 95% Confidence Interval was presented.

End point values	MT-1186	Full Analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	185	185		
Units: Events				
Any TEAE	961	961		
Any TEAE related to study treatment	79	79		
Any severe TEAE	58	58		
Any TESAE	62	62		
TEAE leading to study treatment discontinuation	22	22		
Any TEAE leading to death	13	13		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Death, Tracheostomy or Permanent Assisted Mechanical Ventilation

End point title	Time to Death, Tracheostomy or Permanent Assisted Mechanical Ventilation

End point description:

End point type	Other pre-specified

End point timeframe:

48 Weeks

End point values	MT-1186	Full Analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	185	185		
Units: Events				
Death	14	14		
Tracheostomy	0	0		
Permanent Assisted Mechanical Ventilation	5	5		

Censored	166	166		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	MT-1186
Reporting group description: MT-1186 105mg (2 weeks On/Off)	

Serious adverse events	MT-1186		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 185 (25.95%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	12		
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 185 (1.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Lower limb fracture			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	12 / 185 (6.49%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 2		
Muscle spasticity			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	6 / 185 (3.24%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chronic respiratory failure			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	5 / 185 (2.70%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pleural effusion			

subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	5 / 185 (2.70%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 4		
Restrictive pulmonary disease			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 185 (2.16%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hyponatraemia			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Feeding disorder			
subjects affected / exposed	1 / 185 (0.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	MT-1186		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 185 (66.49%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	15 / 185 (8.11%)		
occurrences (all)	15		
Fall			
subjects affected / exposed	40 / 185 (21.62%)		
occurrences (all)	59		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 185 (7.03%)		
occurrences (all)	18		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	14 / 185 (7.57%) 14		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Salivary Hypersecretion subjects affected / exposed occurrences (all)	 33 / 185 (17.84%) 33 16 / 185 (8.65%) 17 11 / 185 (5.95%) 11		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 16 / 185 (8.65%) 19		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 10 / 185 (5.41%) 12		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 10 / 185 (5.41%) 10 16 / 185 (8.65%) 17		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Muscular weakness	 19 / 185 (10.27%) 19 13 / 185 (7.03%) 14		

subjects affected / exposed	39 / 185 (21.08%)		
occurrences (all)	60		
Musculoskeletal pain			
subjects affected / exposed	10 / 185 (5.41%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2019	Significant changes included in this amendment are summarized below: • Provided additional information to clinical sites regarding dosing cycles/study days • Clarified discrepancies within the protocol • Corrected formatting and spelling throughout
26 February 2020	The amendment clarified discrepancies within the protocol and corrected formatting and spelling throughout.
23 September 2020	Significant changes included in this amendment are summarized below: • Updated with impacts of COVID-19, including delayed completion date, and risks and precautions taken • Clarified discrepancies within the protocol • Updated personnel information • Updated introduction with information from recent studies • Updated with current and revised guidelines • Corrected formatting and spelling throughout
16 April 2021	Significant changes included in this amendment are summarized below: • Contraceptive guidance in Appendix 2 was updated to align with the Germany-specific protocol. • Editorial changes were made to allow PEG/RIG dosing. • The sample size was increased to compensate for potential increased premature terminations due to COVID-19, to ensure at least 100 completers at 48 weeks of treatment. • Due to COVID-19 restrictions related to site visits, it was clarified that formal telehealth would not be used, but instead home nursing visits or telephone calls for questionnaires would be conducted. • It was clarified that any combination of phenylbutyrate and tauroursodeoxycholic acid was prohibited throughout the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported