Clinical trial results:
A Phase 3, Multi-center, Open-label, Safety Extension Study of Oral Edaravone Administered over 96 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Summary

EudraCT number	2020-000376-38
Trial protocol	FR DE IT
Global end of trial date	09 August 2023

Results information

Result version number	v1 (current)
This version publication date	14 August 2024
First version publication date	14 August 2024

Trial information

Trial identification

Sponsor protocol code	MT-1186-A03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04577404
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT: jRCT2041200084

Notes:

Sponsors

Sponsor organisation name	Mitsubishi Tanabe Pharma America Inc.
Sponsor organisation address	525 Washington Boulevard, Suite 1100, Jersey City, New Jersey, United States, 07310
Public contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, +44 2070655000, regulatory@mt-pharma-eu.com
Scientific contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd, +44 2070655000, 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	09 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2023
Global end of trial reached?	Yes
Global end of trial date	09 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of oral edaravone at a dose of 105 mg administered once daily for 10 days out of a 14-day period, followed by a 14-day drug-free period for 96 weeks of treatment or until the drug is commercially available in that country.

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	29 October 2020
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	United States: 38
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	124
EEA total number of subjects	18

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)	84
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 29 Oct 2020 and was completed on 10 Feb 2023. Recruitment was conducted globally in the USA, Canada, Germany, Italy, France and Japan.

Pre-assignment

Screening details:

There was no screening period since the subjects who completed the treatment in the study MT-1186-A01 and met the eligibility criteria were enrolled into this open-label treatment study (MT-1186-A03). Day 1 is equal to the Week 48 visit of the MT-1186-A01 study.

Period 1

Period 1 title	MT-1186-A03 (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open-label study. Therefore, no randomization or blinding is applicable.

Arms

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

Arm description:

Subjects who met eligibility criteria were enrolled into this open-label treatment study (MT-1186-A03) and continued to receive 105 mg of edaravone once daily following an overnight fast, and subjects continued to fast for at least 1 to 2 hours before the next meal (e.g., breakfast). Treatment cycles occurred every 28 days (10 days on study drug out of a 14-day period, followed by 14 days off study drug).

Arm type	Experimental
Investigational medicinal product name	edaravone (MT-1186)
Investigational medicinal product code	MT-1186
Other name	Edaravone
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received an oral dose of edaravone 105 mg suspension. Each treatment cycle included daily dosing for 10 days out of a 14-day period, followed by a 14-day drug-free period. Treatment cycles were every 4 weeks. The dose of edaravone was taken after an overnight fast and subjects continued to fast for at least 1 to 2 hours post-dose before the next meal (e.g., breakfast).

Number of subjects in period 1	MT-1186 105mg (2 weeks On/Off)
Started	124
Completed	49
Not completed	75
Adverse event, serious fatal	1
Consent withdrawn by subject	21
Physician decision	7
Adverse event, non-fatal	31

Other	12
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	MT-1186-A03 (overall period)

Reporting group description: -

Reporting group values	MT-1186-A03 (overall period)	Total	
Number of subjects	124	124	
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)	84	84	
From 65-84 years	40	40	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	59.0		
standard deviation	± 10.1	-	
Gender categorical Units: Subjects			
Female	41	41	
Male	83	83	
Ethinicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	118	118	
Not reported or unknown	4	4	

End points

End points reporting groups

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

Reporting group description:

Subjects who met eligibility criteria were enrolled into this open-label treatment study (MT-1186-A03) and continued to receive 105 mg of edaravone once daily following an overnight fast, and subjects continued to fast for at least 1 to 2 hours before the next meal (e.g., breakfast). Treatment cycles occurred every 28 days (10 days on study drug out of a 14-day period, followed by 14 days off study drug).

Primary: Number of Treatment-Emergent Adverse Events

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

End point description:

End point type	Primary

End point timeframe:

All AEs, regardless of the relationship to IMP, occurring from the time written ICF were obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study.

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: No statistical analyses were performed since the primary end points are the number of TEAEs and the number of patients with TEAEs. Considering the nature of those primary endpoints statistical analysis was not needed.

End point values	MT-1186 105mg (2 weeks On/Off)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Number of Events				
Any TEAE	616			
Any TEAE related to study treatment	17			
Any severe TEAE	60			
Any TESAE	75			
Any TEAE leading to discontinuation	35			
Any TEAE leading to death	19			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Treatment Emergent Adverse Events

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

End point description:

End point type	Primary

End point timeframe:

All AEs, regardless of the relationship to IMP, occurring from the time written ICF were obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study.

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: No statistical analyses were performed since the primary end points are the number of TEAEs and the number of patients with TEAEs. Considering the nature of those primary endpoints statistical analysis was not needed.

End point values	MT-1186 105mg (2 weeks On/Off)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Number of Participants				
Any TEAE	113			
Any TEAE related to study treatment	12			
Any severe TEAE	44			
Any TESAE	52			
Any TEAE leading to discontinuation	28			
Any TEAE leading to death	19			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Adverse Drug Reactions

End point title	Number of Adverse Drug Reactions[3]

End point description:

End point type	Primary

End point timeframe:

All AEs, regardless of the relationship to IMP, occurring from the time written ICF were obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study.

Notes:

[3] - 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: No statistical analyses were performed since the primary end points are the number of ADR and the number of patients with ADR. Considering the nature of those primary endpoints statistical analysis was not needed.

End point values	MT-1186 105mg (2 weeks On/Off)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Number of Events	17			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Adverse Drug Reactions

End point title	Number of Participants with Adverse Drug Reactions[4]

End point description:

End point type	Primary

End point timeframe:

All AEs, regardless of the relationship to IMP, occurring from the time written ICF were obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study.

Notes:

[4] - 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: No statistical analyses were performed since the primary end points are the number of ADR and the number of patients with ADR. Considering the nature of those primary endpoints statistical analysis was not needed.

End point values	MT-1186 105mg (2 weeks On/Off)			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: Number of Participants	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

96 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	MT-1186 105 mg (2 Weeks On/Off)

Reporting group description:

Subjects who met eligibility criteria were enrolled into this open-label treatment study (MT-1186-A03) and continued to receive 105 mg of edaravone once daily following an overnight fast, and subjects continued to fast for at least 1 to 2 hours before the next meal (e.g., breakfast). Treatment cycles occurred every 28 days (10 days on study drug out of a 14-day period, followed by 14 days off study drug).

Serious adverse events	MT-1186 105 mg (2 Weeks On/Off)		
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 124 (41.94%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events			
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	2 / 124 (1.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Accidental death			
subjects affected / exposed	1 / 124 (0.81%)		
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 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asphyxia				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	4 / 124 (3.23%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	9 / 124 (7.26%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory disorder				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	13 / 124 (10.48%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Sputum retention				
subjects affected / exposed	1 / 124 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Assisted suicide			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 124 (0.81%)		
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	6 / 124 (4.84%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			

subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	7 / 124 (5.65%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aerophagia			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 124 (2.42%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Pneumonia staphylococcal			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	3 / 124 (2.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 124 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MT-1186 105 mg (2 Weeks On/Off)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 124 (56.45%)		
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed occurrences (all)	20 / 124 (16.13%) 34		
Nervous system disorders Dysarthria subjects affected / exposed occurrences (all)	 7 / 124 (5.65%) 7		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 16 / 124 (12.90%) 16 8 / 124 (6.45%) 9 7 / 124 (5.65%) 10		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 13 / 124 (10.48%) 14		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 8 / 124 (6.45%) 8 9 / 124 (7.26%) 9		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all)	 18 / 124 (14.52%) 35		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Urinary tract infection	 11 / 124 (8.87%) 13 		

subjects affected / exposed occurrences (all)	8 / 124 (6.45%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2021	Significant changes included in this amendment are summarized below: Study completion delayed due to COVID-19. Removed a reference to the screening in exclusion criterion 2. Removed pregnancy or lactation as exclusion criterion. Added respiratory rate to vital sign measurements. Updated text on clinical pharmacology for studies MT-1186-J04, MT-1186-J05, and MT-1186-J06. Clarified route of administration as oral/PEG/RIG.
23 December 2022	The amendment clarified discrepancies within the protocol and corrected formatting and spelling throughout. Updated the anticipated number of subjects who completed study MT-1186-A01 and who were eligible for this extension study from 100 to 140. Clarified that physical examinations should include neurological examinations. Clarified how the exploratory efficacy analysis would be performed. Added medication compliance assessment to schedule of assessments in place of the eDiary. Revised to reflect completion of study MT-1186-J05 and added information for study MT-1186-Z-101. Updated to allow for PEG/RIG dosing as the subjects' disease progressed to align with removal of the eDiary. Clarified that screen failures cannot be enrolled in the study. Clarified the definition of noncompliance. Clarified that the study can be prematurely terminated and timing of the EOT visit. Clarified expectations due to COVID-19 impacts on study visits and patient safety. Clarified that the use of COVID-19 vaccines are allowed as permitted and concomitant medications. Clarified that subjects discontinue study treatment and that phone calls are to be aligned with clinic visits and are to determine if death, tracheostomy, or permanent assisted mechanical ventilation occurred.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported