



Clinical trial results:

A Phase 3b, Multicenter, Randomized, Double-Blind Study to Evaluate Efficacy and Safety of Oral Edaravone Administered for a Period of 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Summary

EudraCT number	2019-004256-11
Trial protocol	DE IT
Global end of trial date	29 September 2023

Results information

Result version number	v1
This version publication date	03 October 2024
First version publication date	03 October 2024

Trial information

Trial identification

Sponsor protocol code	MT-1186-A02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04569084
WHO universal trial number (UTN)	-
Other trial identifiers	Japan Registry of Clinical Trials (jRCT): jRCT2031200301

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	29 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2023
Global end of trial reached?	Yes
Global end of trial date	29 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the efficacy of the following two dosing regimens of oral edaravone in subjects with ALS based on Combined Assessment of Function and Survival (CAFS) at Week 48:

- Oral edaravone 105 mg administered once daily (regimen denoted as daily) in Cycles 1 through 12
- Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1, and subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off) in Cycles 2 through 12.

Protection of trial subjects:

The study was conducted in accordance with the 2013 (Fortaleza) revision of the 1964 Declaration of Helsinki, Good Clinical Practice (GCP) as required by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regional and local legislation, and standard operating procedures (SOPs) in place at Mitsubishi Tanabe Pharma America, Inc. (MTPA).

Clinical monitoring was conducted to confirm the ethical conduct of the study at the investigational site(s) and was performed according to the SOPs of the Contract Research Organization (CRO) which had been delegated the responsibility for those activities.

The Sponsor had taken out an insurance policy to cover any costs that arise during the research study. Any compensation payable for any injury caused to patients by taking part in this research study would be in line with local guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2020
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: 52
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	United States: 82
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Japan: 128
Country: Number of subjects enrolled	Korea, Republic of: 15
Worldwide total number of subjects	384
EEA total number of subjects	95

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)	256
From 65 to 84 years	128
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited via a variety of methods including, but not limited to, site review of subject records, media advertising, and recruitment vendors, if appropriate. All recruitment material was approved by an IRB/IEC prior to implementation. The recruitment was started from November 2020 and conducted in 96 sites globally.

Pre-assignment

Screening details:

Screening assessments was performed 8 weeks (\pm 7 days) prior to Day 1. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria (e.g., inclusion criteria %FVC \geq 70% versus %FVC \geq 80%). Sites completed a diagnosis verification process for each subject prior to enrollment into the study

Period 1

Period 1 title	MT-1186-A02 (overall) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	edaravone 105 mg (once daily)

Arm description:

Oral edaravone 105 mg administered once daily (regimen denoted as Once Daily) in Cycles 1 through 12

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

Dosage and administration details:

Dose: 105 mg dose

Administration: Oral/percutaneous endoscopic gastrostomy (PEG)/radiologically inserted gastrostomy (RIG) tube. The mode of administration could be switched from oral to PEG/RIG tube dosing dependent on disease progression.

Arm title	edaravone 105mg (2 weeks On/Off)
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Arm description:

Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1. Subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as On/Off) in Cycles 2 through 12

Arm type	Active comparator
Investigational medicinal product name	edaravone (MT-1186)
Investigational medicinal product code	MT-1186
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use, Enteral use

Dosage and administration details:

Dose: 105 mg dose or placebo

Administration: Oral/PEG/RIG tube. The mode of administration could be switched from oral to PEG/RIG tube dosing dependent on disease progression.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use, Enteral use

Dosage and administration details:

Dose: 105 mg dose or placebo

Administration: Oral/PEG/RIG tube. The mode of administration could be switched from oral to PEG/RIG tube dosing dependent on disease progression.

Number of subjects in period 1	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)
Started	192	192
Completed	125	121
Not completed	67	71
Adverse event, serious fatal	2	3
Consent withdrawn by subject	20	21
Physician decision	3	3
Protocol violation	2	1
Adverse event, non-fatal	10	14
Other	3	5
Study terminated by sponsor	26	23
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	edaravone 105 mg (once daily)
Reporting group description:	
Oral edaravone 105 mg administered once daily (regimen denoted as Once Daily) in Cycles 1 through 12	
Reporting group title	edaravone 105mg (2 weeks On/Off)
Reporting group description:	
Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1.	
Subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as On/Off) in Cycles 2 through 12	

Reporting group values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)	Total
Number of subjects	192	192	384
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	134	122	256
From 65-84 years	58	70	128
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	57.9	60.0	
standard deviation	± 10.6	± 9.5	-
Gender categorical			
Units: Subjects			
Female	69	70	139
Male	123	122	245
Race			
Units: Subjects			
White	115	109	224
Black or African American	3	2	5
Asian - Japanese	63	64	127
Asian - Not Japanese	8	13	21
American Indian or Alaska Native	0	1	1
Native Hawaiian or Pacific Islander	0	1	1
Not Reported	0	1	1
Other	3	1	4
Region			
Units: Subjects			
North America - NA	66	65	131
Europe - EU	56	54	110
Asia Pacific - AP	70	73	143

Ethnicity			
Units: Subjects			
Hispanic or Latino	9	5	14
Not Hispanic or Latino	183	187	370
Not reported	0	0	0
Unknown	0	0	0
Hight			
Units: cm			
arithmetic mean	168.50	169.17	
standard deviation	± 9.69	± 9.79	-
Body weight			
Units: kg			
arithmetic mean	69.90	67.78	
standard deviation	± 14.59	± 15.27	-
BMI			
Units: kg/			
arithmetic mean	24.61	23.57	
standard deviation	± 4.27	± 3.83	-

End points

End points reporting groups

Reporting group title	edaravone 105 mg (once daily)
Reporting group description:	
Oral edaravone 105 mg administered once daily (regimen denoted as Once Daily) in Cycles 1 through 12	
Reporting group title	edaravone 105mg (2 weeks On/Off)
Reporting group description:	
Oral edaravone 105 mg administered for 14 days, followed by placebo for 14 days in Cycle 1. Subsequently, repeat oral edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as On/Off) in Cycles 2 through 12	

Primary: CAFS score at Week 48

End point title	CAFS score at Week 48
End point description:	
CAFS results at Week 48. The CAFS score is composed of change of ALSFRS-R score and time to death. A higher CAFS rank indicates a better outcome than does a lower CAFS rank.	
End point type	Primary
End point timeframe:	
at Week 48	

End point values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	191		
Units: points				
number (not applicable)	187.2	184.2		

Statistical analyses

Statistical analysis title	CAFS score at Week 48
Statistical analysis description:	
More than a few death events ($\geq 5\%$ death percentage for all randomized subjects, eg, ≥ 19 death events) were observed in the data review meeting, the primary endpoint analysis using mixed model repeated measures (MMRM) was replaced with the ranking score on CAFS score at Week 48 based on a joint rank score derived from change from baseline in ALSFRS-R score and time to death through Week 48 with analysis of covariance (ANCOVA) specified in the secondary endpoint analysis.	
Comparison groups	edaravone 105 mg (once daily) v edaravone 105mg (2 weeks On/Off)

Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.777
Method	ANCOVA

Secondary: Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ) 40

End point title	Change from baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ) 40
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End point description:

End point type	Secondary
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End point timeframe:

at Week 48

End point values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	125		
Units: Points				
least squares mean (standard error)	2.35 (± 0.25)	1.79 (± 0.25)		

Statistical analyses

Statistical analysis title	Change from baseline in ALSAQ 40
Comparison groups	edaravone 105 mg (once daily) v edaravone 105mg (2 weeks On/Off)
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.793
Method	Mixed Model for Repeated Measures (MMRM)

Secondary: Change from baseline in % slow vital capacity (SVC)

End point title	Change from baseline in % slow vital capacity (SVC)
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End point description:

End point type	Secondary
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End point timeframe:

at Week 48

End point values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	117		
Units: %				
least squares mean (standard error)	-26.94 (± 2.45)	-22.15 (± 2.48)		

Statistical analyses

Statistical analysis title	Change from baseline in % SVC
Comparison groups	edaravone 105 mg (once daily) v edaravone 105mg (2 weeks On/Off)
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169
Method	Mixed Model for Repeated Measures (MMRM)

Secondary: Time to death, tracheostomy, or PAMV (≥ 23 hours/day)

End point title	Time to death, tracheostomy, or PAMV (≥ 23 hours/day)
End point description:	
The median survival time to death, tracheostomy, or PAMV at 50% survival probability timepoint could not be calculated (K-M analysis) in either group due to the low number of events (Once Daily group: 11 events; On/Off group: 17 events), resulting in 181 and 175 censored observations in respective group.	
End point type	Secondary
End point timeframe:	
On Day 1 of study treatment with edaravone through EOT/ET	

End point values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[1] - The median survival time could not be calculated in either group due to the low number of events.

[2] - The median survival time could not be calculated in either group due to the low number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to death or PAMV (≥ 23 hours/day)

End point title	Time to death or PAMV (≥ 23 hours/day)
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End point description:

The median survival time to death or PAMV at 50% survival probability timepoint could not be calculated (K-M analysis) in either group due to the low number of events (Once Daily group: 10 events; On/Off group: 17 events).

End point type	Secondary
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End point timeframe:

On Day 1 of study treatment with edaravone through EOT/ET

End point values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - The median survival time could not be calculated in either group due to the low number of events.

[4] - The median survival time could not be calculated in either group due to the low number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to death

End point title	Time to death
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End point description:

The median survival time to death at 50% survival probability timepoint could not be calculated (K-M analysis) in either group due to the low number of events (Once Daily group: 9 events; On/Off group: 16 events).

End point type	Secondary
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End point timeframe:

On Day 1 of study treatment with edaravone through EOT/ET

End point values	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - The median survival time could not be calculated in either group due to the low number of events.

[6] - The median survival time could not be calculated in either group due to the low number of events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, regardless of the relationship to the IMP, occurring from date of subject's written informed consent until the end of the safety FU period or the withdrawal of the subject from the study, were recorded on an AE form in the eCRF (AE eCRF).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	edaravone 105 mg (once daily)
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Reporting group description: -	
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Reporting group title	edaravone 105 mg (2 weeks On/Off)
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Reporting group description: -	
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Serious adverse events	edaravone 105 mg (once daily)	edaravone 105 mg (2 weeks On/Off)	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 192 (27.08%)	55 / 191 (28.80%)	
number of deaths (all causes)	8	16	
number of deaths resulting from adverse events	8	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Artery dissection			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	3 / 192 (1.56%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunostomy			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 192 (1.04%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Sudden death			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			

subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 192 (1.56%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 192 (0.52%)	3 / 191 (1.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 192 (1.04%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	2 / 192 (1.04%)	5 / 191 (2.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	9 / 192 (4.69%)	10 / 191 (5.24%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 3	0 / 4	
Sputum retention			
subjects affected / exposed	2 / 192 (1.04%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Embedded device			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swallow study			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vital capacity decreased			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Weight decreased			
subjects affected / exposed	1 / 192 (0.52%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 192 (0.52%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Procedural pain			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Benign familial pemphigus			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 192 (0.52%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	1 / 192 (0.52%)	5 / 191 (2.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 192 (0.52%)	2 / 191 (1.05%)	
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	16 / 192 (8.33%)	15 / 191 (7.85%)	
occurrences causally related to treatment / all	0 / 17	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 1	
Salivary hypersecretion			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 192 (2.08%)	4 / 191 (2.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	2 / 192 (1.04%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 192 (0.52%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronavirus infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 192 (0.52%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 192 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	edaravone 105 mg (once daily)	edaravone 105 mg (2 weeks On/Off)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 192 (61.46%)	131 / 191 (68.59%)	
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed occurrences (all)	17 / 192 (8.85%) 23	14 / 191 (7.33%) 18	
Fall subjects affected / exposed occurrences (all)	36 / 192 (18.75%) 57	34 / 191 (17.80%) 64	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	15 / 192 (7.81%) 18	9 / 191 (4.71%) 11	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	12 / 192 (6.25%) 14	10 / 191 (5.24%) 15	
Oedema peripheral subjects affected / exposed occurrences (all)	10 / 192 (5.21%) 10	9 / 191 (4.71%) 9	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	24 / 192 (12.50%) 24	27 / 191 (14.14%) 27	
Diarrhoea subjects affected / exposed occurrences (all)	20 / 192 (10.42%) 25	14 / 191 (7.33%) 15	
Dysphagia subjects affected / exposed occurrences (all)	11 / 192 (5.73%) 12	12 / 191 (6.28%) 13	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	15 / 192 (7.81%) 15	11 / 191 (5.76%) 13	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	11 / 192 (5.73%) 13	8 / 191 (4.19%) 8	
Rash			

subjects affected / exposed occurrences (all)	13 / 192 (6.77%) 16	4 / 191 (2.09%) 4	
Psychiatric disorders			
Depression			
subjects affected / exposed	9 / 192 (4.69%)	10 / 191 (5.24%)	
occurrences (all)	9	10	
Insomnia			
subjects affected / exposed	11 / 192 (5.73%)	14 / 191 (7.33%)	
occurrences (all)	11	14	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 192 (4.17%)	20 / 191 (10.47%)	
occurrences (all)	10	22	
Muscle spasms			
subjects affected / exposed	3 / 192 (1.56%)	10 / 191 (5.24%)	
occurrences (all)	4	13	
Muscular weakness			
subjects affected / exposed	15 / 192 (7.81%)	13 / 191 (6.81%)	
occurrences (all)	36	24	
Musculoskeletal pain			
subjects affected / exposed	10 / 192 (5.21%)	9 / 191 (4.71%)	
occurrences (all)	10	9	
Pain in extremity			
subjects affected / exposed	4 / 192 (2.08%)	10 / 191 (5.24%)	
occurrences (all)	4	10	
Infections and infestations			
COVID-19			
subjects affected / exposed	24 / 192 (12.50%)	26 / 191 (13.61%)	
occurrences (all)	24	26	
Nasopharyngitis			
subjects affected / exposed	11 / 192 (5.73%)	8 / 191 (4.19%)	
occurrences (all)	17	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2021	<ul style="list-style-type: none">• Addition of preliminary results of Study MT-1186-Z-101.• Permission to switch from oral administration to PEG/RIG tube post-baseline due to disease progression.• Updated dosing schedule rationale including the following information: The currently marketed dosing regimen is the On/Off regimen, with patients taking medication for 10 out of 14 days followed by a 14-day medication-free period, resulting in 28-day cycles. This dosing regimen was based on the treatment regimen of edaravone indicated for acute ischemic stroke. The daily dose and the overall design of this study was chosen in conjunction with the FDA as a postmarketing commitment, in hopes of providing patients with a more convenient dosing regimen.• Updated COVID-19 procedures due to COVID-19 restrictions related to site visits and safety assessments such as routine blood sampling or other assessments may be performed at the discretion of the Investigator and the site's abilities, including the performance of complete study visits in the subject's home or questionnaires via telephone.• Permission of COVID-19 and other vaccines that have received emergency use authorization.
24 November 2022	<ul style="list-style-type: none">• Addition of secondary efficacy endpoints:<ul style="list-style-type: none">o Time to death or permanent assisted mechanical ventilation (≥ 23 hours/day)o Time to death• Permission to use AMX0035 for subjects if it becomes commercially available via prescription in their respective country.• Updates based on allowing use of AMX0035:<ul style="list-style-type: none">o Adjustments to primary estimand construction elementso Adjustments to secondary estimand construction elementso Changes to primary analysis: All available ALSFRS-R scores regardless of use of additional/new AMX0035 treatment (ICE1) and all available ALSFRS-R scores up to early discontinuation (ICE2) were included for the primary analysis.o Updated criteria in terms of defined cutoff for minimal number of deaths required for replacing the primary endpoint with the ranking score on CAFS at Week 48.o Addition of sensitivity analyses for the primary efficacy endpointo Addition of supportive analysis for the secondary estimand• Updated study information: Study MT-1186-J03, Study MT-1186-A01• Updates concerning responsibilities for legally authorized representatives (informed consent form)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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01 August 2023	<p>The study was prematurely terminated due to meeting the futility criteria following a pre-planned IA. The futility IA was conducted after 50% of the planned study population (N=190) had completed the 48-week DBT period and assessed the study's primary endpoint and the conditional probability of the study results to show a statistically significant difference in change from baseline in ALSFRS-R total score at Week 48 between the two treatment groups at the final analysis. Through that IA, the IDMC concluded that there was a low conditional probability for the investigational Once Daily regimen to show superiority to the current On/Off regimen as measured by the ALSFRS-R score at study completion, taking into account the results from other efficacy endpoints; therefore, study discontinuation was recommended by the IDMC. Based on the results of the IA and the recommendation from the IDMC, the Sponsor decided to discontinue the study early. As part of this decision, the global, multi-center, double-blind, Phase 3b MT-1186-A04 study, an extension to MT-1186-A02, was also discontinued prematurely. The premature termination of the study was not based on safety concerns.</p>	-
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Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Of the 35.9% subjects who discontinued study treatment, the most common reason for discontinuation was study terminated by Sponsor (12.8% of subjects), which was driven by the decision to terminate the study prematurely due to futility.

Notes: