Clinical trial results:
A Phase 3b, Multicenter, Randomized, Double-blind Extension Study to Evaluate the Continued Efficacy and Safety of Oral Edaravone Administered for an Additional Period of up to 48 Weeks Following Study MT-1186-A02 in Subjects with Amyotrophic Lateral Sclerosis (ALS)

Summary

EudraCT number	2021-003900-42
Trial protocol	DE IT
Global end of trial date	05 October 2023

Results information

Result version number	v1 (current)
This version publication date	03 October 2024
First version publication date	03 October 2024

Trial information

Trial identification

Sponsor protocol code	MT-1186-A04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05151471
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT: 2071210117

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	05 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2023
Global end of trial reached?	Yes
Global end of trial date	05 October 2023
Was the trial ended prematurely?	Yes

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 amyotrophic lateral sclerosis (ALS) based on the time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in Revised ALS Functional Rating Score (ALSFRS-R) or death, whichever happens first, over the course of the study or until the oral Edaravone is commercially available in that country:
- Oral Edaravone 105 mg administered once daily
- Oral Edaravone 105 mg administered for 10 days followed by placebo for 18 days (regimen denoted as on/off).

Protection of trial subjects:

The Investigator ensured that this study was conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study was conducted in accordance with GCP requirements described in the current revision of ICH of Technical Requirements of Pharmaceuticals for Human Use Guidelines. This study was carried out in accordance with regional and local legal requirements. Before the first subject was enrolled in the study, all ethical and legal requirements were met.
Prior to undergoing any study-specific procedure, all subjects or their Legally authorized representative (LAR) must consent in writing to participate. An ICF was given to each subject, which contained all regulatory required elements, all ICH-required elements, and data protection information, when applicable, in a language that is understandable to the subject or their LAR.
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	11 January 2022
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 upon completion of the MT-1186-A02 study. Only subjects who were eligible for the study based upon their Week 48 procedures from the MT-1186-A02 study were enrolled.
The recruitment was conducted in North America, Europe, and Asia Pacific and the first subject was screened on 11 January 2022.

Pre-assignment

Screening details:

The duration of study for individual subjects comprised of a Screening/Day 1, the Week 48 study procedures from Study MT-1186-A02 were used as the Screening/entry criteria for Study MT-1186-A04.

Period 1

Period 1 title	MT-1186-A02(overall)
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	A02_edaravone 105 mg (once daily)

Arm description:

Oral edaravone 105 mg administered once daily (regimen denoted as Once Daily) from MT-1186-A02 Baseline to Week 96 (A04 Week 48).

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	Enteral use , Oral use

Dosage and administration details:

Oral edaravone 105 mg administered once daily

Arm title	A02_edaravone 105 mg (on/off)

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) from MT-1186-A02 Baseline to Week 96 (A04 Week 48).

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	Enteral use , Oral use

Dosage and administration details:

Oral edaravone 105 mg for 14 days, followed by placebo for 14 days. Subsequently, repeat oral edaravone 105 mg for 10 days followed by placebo for 18 days in Cycles 2 through 12 (48 weeks).

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

Dosage and administration details:

Oral edaravone 105 mg for 14 days, followed by placebo for 14 days. Subsequently, repeat oral edaravone 105 mg for 10 days followed by placebo for 18 days in Cycles 2 through 12 (48 weeks).

Number of subjects in period 1	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (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
Adverse event, non-fatal	10	14
Other	3	5
Study terminated by sponsor	26	23
Lost to follow-up	1	1
Protocol deviation	2	1

Period 2

Period 2 title	MT-1186-A04 (overall)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

During the double-blind treatment period, neither the subject nor the Investigator site personnel knew which treatment was being taken. Each subject maintained their unique randomization number assigned from Study MT-1186-A02. The codes were only accessible to authorized IVRS/IWRS users.

Arms

Are arms mutually exclusive?	Yes
Arm title	A04_edaravone 105 mg (once daily)

Arm description:

Oral edaravone 105 mg dose once daily in each 28-day cycle for up to 48 weeks or until the drug is commercially available in that country. Subjects who met study MT-1186-A04 eligibility criteria, continued in the same treatment group/regimen that they were in during Study MT-1186-A02.

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	Enteral use , Oral use

Dosage and administration details:

Oral edaravone 105 mg administered once daily

Arm title	A04_edaravone 105 mg (on/off)

Arm description:

Oral edaravone 105 mg dose for 10 days followed by 18-day placebo (regimen denoted as on/off) in each 28-day cycle for up to 48 weeks or until the drug is commercially available in that country. Subjects who met study MT-1186-A04 eligibility criteria, continued in the same treatment group/regimen that they were in during Study MT-1186-A02.

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:

Oral edaravone 105 mg for 14 days, followed by placebo for 14 days. Subsequently, repeat oral edaravone 105 mg for 10 days followed by placebo for 18 days in Cycles 2 through 12 (48 weeks).

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:

Oral edaravone 105 mg for 14 days, followed by placebo for 14 days. Subsequently, repeat oral edaravone 105 mg for 10 days followed by placebo for 18 days in Cycles 2 through 12 (48 weeks).

Number of subjects in period 2[1]	A04_edaravone 105 mg (once daily)	A04_edaravone 105 mg (on/off)
Started	104	98
Completed	24	24
Not completed	80	74
Adverse event, serious fatal	1	-
Consent withdrawn by subject	7	9
Adverse event, non-fatal	21	16
Other	2	1
Study terminated by sponsor	49	47
Lost to follow-up	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only Subjects who completed MT-1186-A02 and signed ICF for rollover into MT-1186-A04 were able to join to MT-1186-A04.

Baseline characteristics

Reporting groups	
Reporting group title	A02_edaravone 105 mg (once daily)
Reporting group description:	
Oral edaravone 105 mg administered once daily (regimen denoted as Once Daily) from MT-1186-A02 Baseline to Week 96 (A04 Week 48).	
Reporting group title	A02_edaravone 105 mg (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) from MT-1186-A02 Baseline to Week 96 (A04 Week 48).	

Reporting group values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (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
Country Units: Subjects			
United States	38	44	82
Canada	28	21	49

Germany	24	28	52
Italy	23	20	43
Switzerland	9	6	15
Japan	63	65	128
South Korea	7	8	15
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
Height 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	A02_edaravone 105 mg (once daily)
Reporting group description:	
Oral edaravone 105 mg administered once daily (regimen denoted as Once Daily) from MT-1186-A02 Baseline to Week 96 (A04 Week 48).	
Reporting group title	A02_edaravone 105 mg (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) from MT-1186-A02 Baseline to Week 96 (A04 Week 48).	
Reporting group title	A04_edaravone 105 mg (once daily)
Reporting group description:	
Oral edaravone 105 mg dose once daily in each 28-day cycle for up to 48 weeks or until the drug is commercially available in that country. Subjects who met study MT-1186-A04 eligibility criteria, continued in the same treatment group/regimen that they were in during Study MT-1186-A02.	
Reporting group title	A04_edaravone 105 mg (on/off)
Reporting group description:	
Oral edaravone 105 mg dose for 10 days followed by 18-day placebo (regimen denoted as on/off) in each 28-day cycle for up to 48 weeks or until the drug is commercially available in that country. Subjects who met study MT-1186-A04 eligibility criteria, continued in the same treatment group/regimen that they were in during Study MT-1186-A02.	

Primary: Time to at least a 12-point Decrease in ALSFRS-R or Death

End point title	Time to at least a 12-point Decrease in ALSFRS-R or Death
End point description:	
The primary efficacy endpoint assessed the time from the randomization date in Study MT- 1186-A02 to at least a 12-point decrease in ALSFRS-R or death, whichever happened first.	
End point type	Primary
End point timeframe:	
96 weeks	

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	82		
Units: months				
median (confidence interval 80%)	13.90 (13.40 to 16.59)	15.05 (13.80 to 16.62)		

Statistical analyses

Statistical analysis title	Time to ≥12-point Decrease in ALSFRS-R or Death
Comparison groups	A02_edaravone 105 mg (once daily) v A02_edaravone 105 mg (on/off)

Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Logrank

Secondary: Change in the ALSAQ 40 score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

End point title	Change in the ALSAQ 40 score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

End point description:

End point type	Secondary

End point timeframe:

Up to 96 weeks

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	27		
Units: points				
least squares mean (standard error)	54.83 (± 4.05)	57.91 (± 4.13)		

Statistical analyses

Statistical analysis title	Change in the ALSAQ40 score at all visits
Comparison groups	A02_edaravone 105 mg (once daily) v A02_edaravone 105 mg (on/off)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.591
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Mixed Model for Repeated Measures (MMRM)

Secondary: Change in ALSFRS-R score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

End point title	Change in ALSFRS-R score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

End point description:

End point type	Secondary

End point timeframe:
Up to 96 weeks

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	29		
Units: points				
least squares mean (standard error)	-18.21 (± 1.31)	-20.95 (± 1.32)		

Statistical analyses

Statistical analysis title	Changes from Baseline in ALSFRS-R Total Score
Comparison groups	A02_edaravone 105 mg (once daily) v A02_edaravone 105 mg (on/off)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142
Method	Mixed Model for Repeated Measures (MMRM)

Secondary: The CAFS score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

End point title	The CAFS score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

End point description:

End point type	Secondary

End point timeframe:
Up to week 96

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	191		
Units: Rank				
number (not applicable)	200.8	181.6		

Statistical analyses

Statistical analysis title	The CAFS score at all visits from baseline
Comparison groups	A02_edaravone 105 mg (once daily) v A02_edaravone 105 mg (on/off)
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	ANCOVA

Secondary: Time from the randomization date in Study MT-1186-A02 to death, tracheostomy, or PAMV (≥23 hours/day)

End point title	Time from the randomization date in Study MT-1186-A02 to death, tracheostomy, or PAMV (≥23 hours/day)

End point description:

The median survival for the time to death could not be calculated due to the low number of events (only 33 and 32 events of death, tracheostomy, or PAMV in the Once Daily and On/Off groups, respectively), resulting in 159 and 160 censored observations in respective group.

End point type	Secondary

End point timeframe:

From the randomization date in Study MT-1186-A02 through EOT/ET in Study MT-1186-A04

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time from the randomization date in Study MT-1186-A02 to death or PAMV (≥23 hours/day)

End point title	Time from the randomization date in Study MT-1186-A02 to death or PAMV (≥23 hours/day)

End point description:

The median survival for the time to death could not be calculated due to the low number of events (only 30 and 31 events of death or PAMV in the Once Daily and On/Off groups, respectively), resulting in 162 and 161 censored observations in respective group.

End point type	Secondary

End point timeframe:

From the randomization date in Study MT-1186-A02 through EOT/ET in Study MT-1186-A04

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time from the randomization date in Study MT-1186-A02 to death

End point title	Time from the randomization date in Study MT-1186-A02 to death

End point description:

The median survival for the time to death could not be calculated due to the low number of events (only 24 and 28 events of death in the Once Daily and On/Off groups, respectively), resulting in 168 and 164 censored observations in respective group.

End point type	Secondary

End point timeframe:

From the randomization date in Study MT-1186-A02 through EOT/ET in Study MT-1186-A04

End point values	A02_edaravone 105 mg (once daily)	A02_edaravone 105 mg (on/off)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

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

[6] - The median survival for the time to death could not be calculated 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 and SAEs that occur from the time written ICF was obtained until the end of the Safety Follow-up Period or the withdrawal of the subject from the study. Safety assessments made on the data from MT-1186-A04.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	edaravone 105 mg (once daily)
Reporting group description: -	
Reporting group title	edaravone 105mg (2 weeks On/Off)

Reporting group description: -

Serious adverse events	edaravone 105 mg (once daily)	edaravone 105mg (2 weeks On/Off)	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 104 (31.73%)	27 / 98 (27.55%)	
number of deaths (all causes)	15	12	
number of deaths resulting from adverse events	13	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	0 / 104 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	1 / 104 (0.96%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thermal burn			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	4 / 104 (3.85%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
General disorders and administration site conditions			
Death			

subjects affected / exposed	2 / 104 (1.92%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	14 / 104 (13.46%)	5 / 98 (5.10%)	
occurrences causally related to treatment / all	0 / 14	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asphyxia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 104 (0.96%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (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	2 / 104 (1.92%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory disorder			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 104 (0.96%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	10 / 104 (9.62%)	10 / 98 (10.20%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 6	0 / 5	
Sputum retention			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric symptom			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (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	2 / 104 (1.92%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 104 (1.92%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 104 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 104 (0.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 105mg (2 weeks On/Off)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 104 (23.08%)	25 / 98 (25.51%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 104 (7.69%)	13 / 98 (13.27%)	
occurrences (all)	13	24	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 104 (6.73%)	6 / 98 (6.12%)	
occurrences (all)	7	6	
Diarrhoea			
subjects affected / exposed	4 / 104 (3.85%)	5 / 98 (5.10%)	
occurrences (all)	8	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 104 (4.81%)	5 / 98 (5.10%)	
occurrences (all)	5	5	
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 104 (5.77%)	1 / 98 (1.02%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2022	• Secondary Efficacy Endpoints were updated to clarify timing of endpoint analyses. • Exploratory efficacy endpoints were updated to clarify timing of endpoint analyses. • Updated to allow subjects to remain in a sitting position. • Updated to allow for when corrected QT interval is unavailable. • Updated pregnancy test requirements. • Updated compliance definition and recording requirements. • Updated menopause confirmation requirements.
20 October 2022	• Updates based on AMX0035 use: • Updates based on allowing AMX0035 use for subjects if it becomes commercially available via prescription in their respective country. AMX0035 was to be taken at least 1 hour after MT-1186/oral edaravone dosing. • The primary estimand construction elements were: Treatment of interest, population, variable, ICE handling strategy and population-level summary. • The secondary estimand was to be tested as supportive analysis for the primary endpoint. • Supportive analysis for the secondary estimand was updated from sensitivity analysis. • Updated secondary efficacy endpoints: • Time from the randomization

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2023	The MT-1186-A02 study was prematurely terminated as it met the futility criteria following a pre-planned interim futility analysis. As a result of the pre-planned futility analysis of MT-1186-A02, the Sponsor endorsed the IDMC recommendation and decided to also terminate the MT-1186-A04 study.	-

Notes:

Limitations and caveats

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

Due to the early termination of the study, a low number of the subjects completed the 48-week DBT period of MT-1186-A04. Of the subjects who discontinued study treatment, the most common reason for discontinuation was study terminated by Sponsor.

Notes: